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     FILE 'HCAPLUS' ENTERED AT 12:47:58 ON 14 JAN 2005
L1            1 (US20040082637 OR US6667302 OR US20020151575)/PN
              E WO1998-US27822/AP,PRN
L2            1 WO1998-US27822/AP,PRN
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L3            1 US1997-070287P/AP,PRN
L4            1 L1-3

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L7            1 (US20040082637 OR US6667302 OR US20020151575)/PN
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L9            1 US1997-070287P/AP,PRN
L10           1 L7-9

=> b hcap
FILE 'HCAPLUS' ENTERED AT 12:51:44 ON 14 JAN 2005
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FILE COVERS 1907 - 14 Jan 2005  VOL 142 ISS 3
FILE LAST UPDATED: 12 Jan 2005  (20050112/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d all l4

L4   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1999:460416  HCAPLUS
DN   131:87914
ED   Entered STN:  28 Jul 1999
TI   Heterocyclic topoisomerase poisons, namely 2-(benzimidazol-5-
     yl)benzimidazoles
IN   Lavoie, Edmond J.; Kim, Jun Sung; Liu, Leroy Fong
PA   Rutgers, the State University of New Jersey, USA
SO   PCT Int. Appl., 29 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C07D403-04
     ICS  A61K031-415
CC   28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
     Section cross-reference(s): 1, 7
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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PI   WO 9933824           A1    19990708    WO 1998-US27822        19981230 <--
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
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TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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AU 9920220	A1	19990719	AU 1999-20220	19981230	<--
AU 753268	B2	20021010			
EP 1044199	A1	20001018	EP 1998-965021	19981230	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
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US 2002151575	A1	20021017	US 2001-869141	20010613	<--
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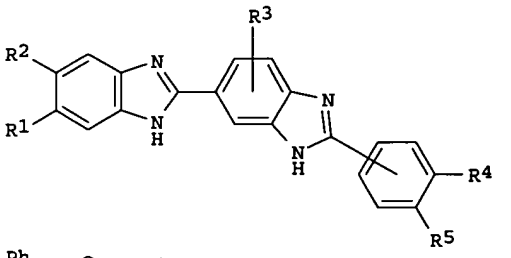
PRAI US 1997-70287P	P	19971231	<--		
WO 1998-US27822	W	19981230	<--		
US 2001-869141	A3	20010613			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 9933824	ICM	C07D403-04	
	ICS	A61K031-415	
WO 9933824	ECLA	C07D235/20; C07D403/14+239+235C+235C; C07D403/14+249+235C+235C	<--
US 2002151575	ECLA	C07D235/20; C07D403/14+239+235C+235C; C07D403/14+249+235C+235C	<--
US 2004082637	ECLA	C07D235/20; C07D403/14+239+235C+235C; C07D403/14+249+235C+235C	<--

OS MARPAT 131:87914

GI



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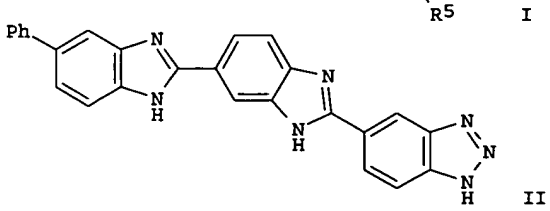


II

AB The invention provides title compds. I [R1, R2 = H, alkyl, cycloalkyl, alkoxy, (un)substituted (hetero)aryl, etc; or R1R2 = benzo, methylenedioxy; R3 = H, alkyl, cycloalkyl, alkoxy, OH, CF3O, halo, etc.; R4R5 = 3- to 5-atom ring-forming chain containing .gtoreq.1 NH group, and as further units O (except peroxides), S, N(X), C, or C(O), where X = null, H, O, alkyl, Ph, or PhCH2], as well as their pharmaceutically acceptable salts, pharmaceutical compns., and use of any of these to treat cancer. For instance, 5-phenyl-2-[2-(3,4-dinitrophenyl)benzimidazol-5-yl]benzimidazole was hydrogenated over Pd/C to give the 3,4-diamino compound, which underwent diazotization with concomitant cyclization to give title compound II. Two example compds. potently inhibited topoisomerase I in vitro, and also exhibited cytotoxic activity against RPMI 8402 cancer cells and camptothecin-resistant CPT-K5 cells in vitro.

ST heterocyclic topoisomerase poison benzimidazolylbenzimidazole prepn

IT Antitumor agents
Cytotoxic agents
(preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)

IT Antitumor agents

(solid tumor, treatment; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
IT 167959-27-5, 5-Phenyl-2-[2-(benzimidazol-5-yl)benzimidazol-5-yl]benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparison compound; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
IT 230308-98-2P, 5-Phenyl-2-[2-(quinoxalin-6-yl)benzimidazol-5-yl]benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(comparison compound; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
IT 230308-95-9P, 5-Phenyl-2-[2-(3,4-diaminophenyl)benzimidazol-5-yl]benzimidazole
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
IT 144-62-7, Ethanedioic acid, reactions 517-21-5, Glyoxal disodium bisulfite 192879-72-4, 5-Phenyl-2-[2-(3,4-dinitrophenyl)benzimidazol-5-yl]benzimidazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
IT 230308-96-0P, 5-Phenyl-2-[2-(1H-benzotriazol-5-yl)benzimidazol-5-yl]benzimidazole 230308-97-1P, 5-Phenyl-2-[2-(1,2,3,4-tetrahydro-2,3-dioxoquinoxalin-6-yl)benzimidazol-5-yl]benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compound; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Arznad; ARZNEIM-FORSCH 1974, V24(12), P1927
(2) Goldman, G; BIOCHEMISTRY 1997, V36(21), P6488 HCAPLUS
(3) Heinz, L; US 3538097 A 1970
(4) Kim, J; J MED CHEM 1996, V39(4), P992 HCAPLUS
(5) Kim, J; JOURNAL OF MEDICINAL CHEMISTRY 1997, V40(18), P2818 HCAPLUS
(6) Lavoie, E; WO 9636612 A 1996 HCAPLUS
(7) Lavoie, E; WO 9831673 A 1998 HCAPLUS
(8) Loewe, H; Basic substituted 2,6-bisbenzimidazole derivatives, a novel series of substances with chemotherapeutic activity 1975, 17, HCAPLUS
(9) Sun, Q; BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1994, V4(24), P2871 HCAPLUS

=> b reg
FILE 'REGISTRY' ENTERED AT 12:51:51 ON 14 JAN 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 12 JAN 2005 HIGHEST RN 812631-13-3
DICTIONARY FILE UPDATES: 12 JAN 2005 HIGHEST RN 812631-13-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

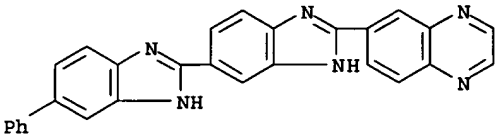
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer

to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide l6 tot

L6 ANSWER 1 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN **230308-98-2** REGISTRY
CN Quinoxaline, 6-(5-phenyl[2,5'-bi-1H-benzimidazol]-2'-yl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Phenyl-2-[2-(quinoxalin-6-yl)benzimidazol-5-yl]benzimidazole
FS 3D CONCORD
MF C28 H18 N6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)



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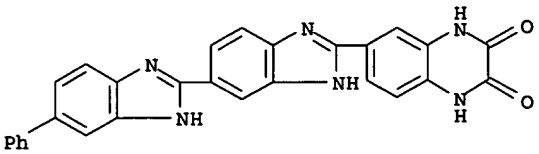
3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN **230308-97-1** REGISTRY
CN 2,3-Quinoxalinedione, 1,4-dihydro-6-(5-phenyl[2,5'-bi-1H-benzimidazol]-2'-yl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Phenyl-2-[2-(1,2,3,4-tetrahydro-2,3-dioxoquinoxalin-6-yl)benzimidazol-5-yl]benzimidazole
FS 3D CONCORD
MF C28 H18 N6 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)



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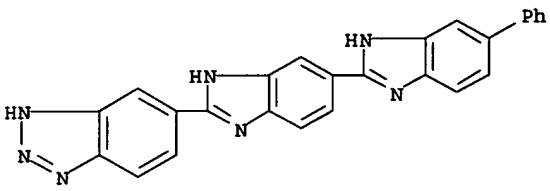
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 3 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN **230308-96-0** REGISTRY
CN 1H-Benzotriazole, 5-(5-phenyl[2,5'-bi-1H-benzimidazol]-2'-yl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Phenyl-2-[2-(1H-benzotriazol-5-yl)benzimidazol-5-yl]benzimidazole
FS 3D CONCORD
MF C26 H17 N7

SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)



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3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 4 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN **230308-95-9** REGISTRY
CN 1,2-Benzenediamine, 4-(5-phenyl[2,5'-bi-1H-benzimidazol]-2'-yl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Phenyl-2-[2-(3,4-diaminophenyl)benzimidazol-5-yl]benzimidazole
FS 3D CONCORD
MF C26 H20 N6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
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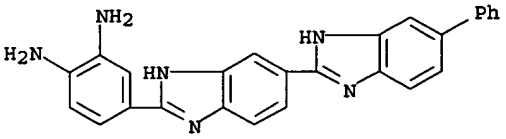
RL.NP Roles from non-patents: PREP (Preparation); RACT (Reactant or reagent)



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4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 5 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN **192879-72-4** REGISTRY
CN 2,5'-Bi-1H-benzimidazole, 2'-(3,4-dinitrophenyl)-5-phenyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Phenyl-2-[2-(3,4-dinitrophenyl)benzimidazol-5-yl]benzimidazole
FS 3D CONCORD
MF C26 H16 N6 O4
SR CA
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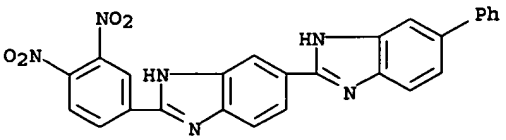

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4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 6 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN **167959-27-5** REGISTRY
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OTHER NAMES:
CN 5-Phenyl-2-[2-(benzimidazol-5-yl)benzimidazol-5-yl]benzimidazole
FS 3D CONCORD
MF C27 H18 N6
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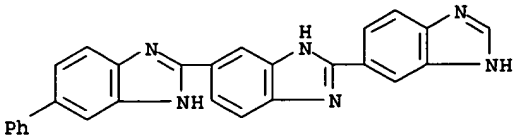
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)



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16 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 7 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN **143180-75-0** REGISTRY
CN Isomerase, deoxyribonucleate topo-, I (9CI) (CA INDEX NAME)
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CN Deoxyribonucleate topoisomerase I
CN DNA topoisomerase I
CN Topiosomerase I
MF Unspecified
CI MAN
SR CA
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DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
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2318 REFERENCES IN FILE CA (1907 TO DATE)
58 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2333 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 8 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN **517-21-5** REGISTRY
CN 1,2-Ethanedisulfonic acid, 1,2-dihydroxy-, disodium salt (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:

CN Disodium 1,2-dihydroxy-1,2-ethanedisulfonate
CN Glyoxal disodium bisulfite
CN Glyoxal-sodium bisulfite adduct (1:2)
CN NSC 18262
CN Sodium glyoxal bisulfite
DR 98769-15-4, 136369-95-4, 69098-87-9, 70975-10-9, 152159-10-9, 41266-48-2, 335081-70-4
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(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Journal; Patent; Report
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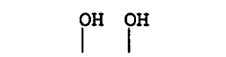
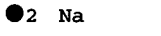
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
CRN (18381-20-9)





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3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L6 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN **144-62-7** REGISTRY
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OTHER CA INDEX NAMES:
CN Oxalic acid (8CI)
OTHER NAMES:
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CN Aquisal
CN NSC 132055
CN NSC 151956
CN NSC 62774
CN NSC 76990
CN Oxagel
CN Ultraplast Activate S 52
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CI COM
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(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
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DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Preprint; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
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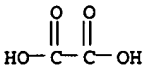

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L10 ANSWER 1 OF 1 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1999-405477 [34] WPIX
DNC C1999-119773
TI Bibenzimidazole derivatives useful for treating solid mammalian tumors or hematological malignancies.
DC B02
IN KIM, J S; LAVOIE, E J; LIU, L F; LA VOIE, E J
PA (KIMS-I) KIM S; (LAVO-I) LAVOIE E J; (LIUL-I) LIU L F; (RUTF) UNIV RUTGERS STATE NEW JERSEY; (KIMJ-I) KIM J S

CYC 85
PI WO 9933824 A1 19990708 (199934)* EN 27 C07D403-04
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AU 9920220 A 19990719 (199951) C07D403-04
EP 1044199 A1 20001018 (200053) EN C07D403-04
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CN 1299358 A 20010613 (200158) C07D403-04
MX 2000006499 A1 20010201 (200168) A61K031-415
JP 2002509858 W 20020402 (200225) 31 C07D235-06
US 2002151575 A1 20021017 (200270) A61K031-4184 <--
AU 753268 B 20021010 (200279) C07D403-04
US 6667302 B2 20031223 (200408) C07D403-10 <--
US 2004082637 A1 20040429 (200429) A61K031-4184 <--
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PRAI **US 1997-70287P 19971231**; US 2001-869141 20010613; US 2003-690800 20031021
IC ICM A61K031-415; A61K031-4184; C07D235-06; C07D403-04; C07D403-10
ICS A61P035-00; C07D235-04; C07D403-02
AB WO 9933824 A UPAB: 19990825
NOVELTY - Novel bibenzimidazole derivatives are topoisomerase I inhibitors and effective cytotoxic agents against cancer cells, including drug-resistant cancer cells.
DETAILED DESCRIPTION - Bibenzimidazole derivatives of formula (I) and their salts are new.
R1, R2 = H, 1-6C alkyl, 3-6C cycloalkyl, 1-6C alkoxy, NO2, OH, 1-6C haloalkyl, OCF3, halo, 3-6C cycloalkyl-1-6C alkyl, 1-6C alkanoyl, hydroxy-1-6C alkyl, 1-6C alkoxycarbonyl, 1-6C alkylthio, 2-6C alkanoyloxy or aryl or heteroaryl (both optionally substituted by 1-3 Q); or R1 + R2 = methylene dioxy or benzo (optionally substituted by 1-3 Q);
Q = 1-6C alkyl, 3-6C cycloalkyl, 1-6C alkoxy, NO2, OH, 1-6C halo alkyl, OCF3, 3-6C cycloalkyl-1-6C alkyl, 1-6C alkanoyl, hydroxy-1-6C alkyl, 1-6C alkoxy-carbonyl, 1-6C alkylthio, 2-6C alkanoyloxy or halo;
R3 = H, 1-6C alkyl, 3-6C cycloalkyl, 1-6C alkoxy, NO2, OH, halo- 1-6C alkyl, OCF3, 3-6C cycloalkyl-1-6C alkyl, 1-6C alkanoyl, hydroxy-1-6C alkyl, 1-6C alkoxycarbonyl, 1-6C alkylthio, 2-6C alkanoyl-oxy or halo;
R4 + R5 = 3-5 membered saturated or unsaturated chain comprising non-peroxide oxygen, sulfur, N(X) and carbon, optionally substituted by oxo;
X = absent or is H, O, 1-4C alkyl, phenyl or benzyl; in which at least one (e.g.. 1 or 2) of the chain members is NH; provided that R4 + R5 are not NH-CH=N.
ACTIVITY - Cytostatic. 5-Phenyl-2'-(benzotriazol-5-yl)-bibenzimidazole showed in vitro cytotoxicity against RPMI 8402 cancer cells and camptothecin resistant CPT-K5 cells with IC50 values of 0.47 and 0.47 microns, respectively.
MECHANISM OF ACTION - Toposomerase-I Inhibitor.
USE - (I) are potent topoisomerase I poisons. They exhibit cytotoxic activity against RPMI 8402 cancer cells and camptothecin resistant CPT-K5 cells. (I) are useful as cytotoxic agents for the treatment of cancers, and in particular, solid mammalian tumors or hematological malignancies. (I) are also useful as pharmacological tools for in vitro and in vivo study of topoisomerase function and activity.
Dwg.0/2
FS CPI

FA AB; GI; DCN
MC CPI: B06-D05; B06-H; B12-K04; B14-D09; B14-H01

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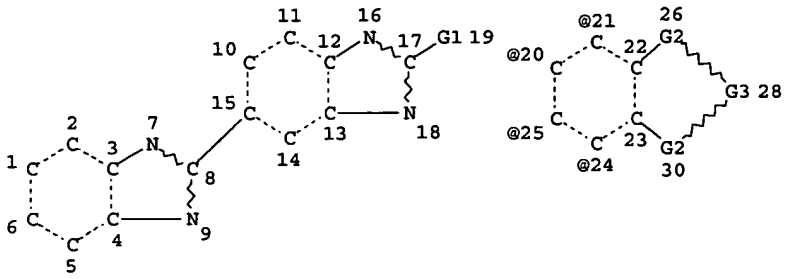


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L18          16 E3
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L19          55 E3
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                E LIU LEROY/AU
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L22       28252 RUTGERS/CS,PA
L23             QUE (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?CARCINOGEN? OR ?MALIGN
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L25          16 L24 AND L16-22
L26          20 L24 NOT L25
L27           3 L26 AND L23
L28          17 L26 NOT L27

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L25  ANSWER 1 OF 16  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2003:941009  HCAPLUS
DN   140:280814
ED   Entered STN:  03 Dec 2003
TI   Effects of topoisomerases inhibitors protoberberine on Leishmania donovani
     growth, macrophage function, and infection
AU   Marquis, Jean-Francois; Makhey, Darshan; LaVoie, Edmond J.;
     Olivier, Martin
CS   Departement de Biologie Medicale, Faculte de Medecine, Centre de Recherche
     en Infectiologie du CHUQ, Universite Laval, Sainte-Foy, QC, G1V 4G2, Can.
SO   Journal of Parasitology (2003), 89(5), 1048-1052
     CODEN: JOPAA2; ISSN: 0022-3395
```

PB American Society of Parasitologists
DT Journal
LA English
CC 1-5 (Pharmacology)
AB DNA topoisomerases play a pivotal role in the regulation of cell division. Inhibition of Leishmania spp. topoisomerases represents an alternative to control parasite growth. Cancer research led to the development of several potent topoisomerase inhibitors such as topoisomerase 1, topoisomerase 17, or both (monobenzimidazole, terbenzimidazole, and protoberberine alkaloid-related compds.) that are effective antitumor agents. In the present study, we evaluated the efficacy of these compds. against Leishmania spp. growth in vitro. Some protoberberine compds. showed pronounced antileishmanial activity and were selected for further anal. in macrophages. These compds. did not affect macrophage viability and only slightly reduced macrophage nitric oxide generation in response to interferon-.gamma.. Moreover, exposure of infected macrophages to these compds. significantly reduced parasite loads. Collectively, our data suggest that protoberberine-related compds. have powerful antileishmania action and that minor structural variations among them can substantially improve their activity to restrict Leishmania spp. infection in vitro.
ST topoisomerase inhibitor protoberberine deriv Leishmania donovani
IT Protozoacides
(leishmanicides; topoisomerase inhibitors protoberberine derivs. effects on Leishmania donovani growth, macrophage function, and infection)
IT Leishmania donovani
Macrophage
Phagocyte
(topoisomerase inhibitors protoberberine derivs. effects on Leishmania donovani growth, macrophage function, and infection)
IT 10102-43-9, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(topoisomerase inhibitors protoberberine derivs. effects on Leishmania donovani growth, macrophage function, and infection)
IT 483-15-8 2086-83-1 3486-67-7 6872-81-7 17388-19-1 19716-66-6 35989-93-6 96954-35-7 **167959-21-9**, Terbenzimidazole 180077-22-9 180077-24-1 180077-31-0 180077-32-1 180077-33-2 286000-57-5 675881-79-5 675881-80-8 675881-81-9 675881-82-0 675881-83-1
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topoisomerase inhibitors protoberberine derivs. effects on Leishmania donovani growth, macrophage function, and infection)
IT 19716-69-9D, Protoberberine, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topoisomerase inhibitors protoberberine derivs. effects on Leishmania donovani growth, macrophage function, and infection)
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RE
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IT 167959-21-9, Terbenzimidazole
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topoisomerase inhibitors protoberberine derivs. effects on Leishmania donovani growth, macrophage function, and infection)
RN 167959-21-9 HCAPLUS
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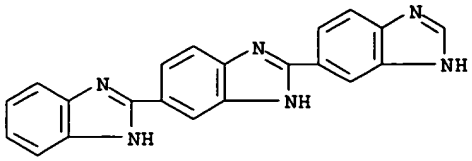

L25 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:679625 HCAPLUS
DN 140:280441
ED Entered STN: 31 Aug 2003
TI Defining the molecular interactions that are important for the poisoning of human topoisomerase I by benzimidazoles and terbenzimidazoles
AU Pilch, Daniel S.; Liu, Hsing-Yin; Li, Tsai-Kun; Kerrigan, John E.; **LaVoie, Edmond J.**; Barbieri, Christopher M.
CS Germany
SO Small Molecule DNA and RNA Binders (2003), Volume 2, 576-608. Editor(s): Demeunynck, Martine; Bailly, Christian; Wilson, W. David. Publisher: Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.
CODEN: 69EKGP; ISBN: 3-527-30595-5
DT Conference; General Review
LA English
CC 1-0 (Pharmacology)
AB A review focuses on the mol. interactions that are important in the poisoning of human topoisomerase type I by antitumor benzimidazole-containing compds., with emphasis on derivs. that contain either one or three benzimidazole functionalities.
ST review human topoisomerase I poisoning benzimidazole terbenzimidazole; antitumor benzimidazole topoisomerase I poisoning review
IT Antitumor agents
Human
Molecular association
Neoplasm
(defining the mol. interactions that are important for poisoning of human topoisomerase I by antitumor benzimidazoles and terbenzimidazoles)
IT 143180-75-0, DNA Topoisomerase I
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(defining the mol. interactions that are important for poisoning of human topoisomerase I by antitumor benzimidazoles and terbenzimidazoles)
IT 51-17-2D, Benzimidazole, analogs **167959-21-9D**, Terbenzimidazole, analogs
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(defining the mol. interactions that are important for poisoning of human topoisomerase I by antitumor benzimidazoles and terbenzimidazoles)
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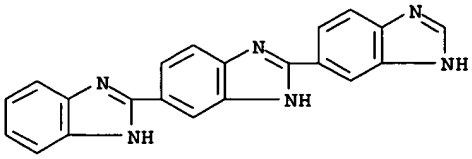
IT **167959-21-9D**, Terbenzimidazole, analogs
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(defining the mol. interactions that are important for poisoning of human topoisomerase I by antitumor benzimidazoles and terbenzimidazoles)

RN 167959-21-9 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole (9CI) (CA INDEX NAME)



L25 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:840668 HCAPLUS
DN 134:95134
ED Entered STN: 01 Dec 2000
TI Topoisomerase I inhibition and cytotoxicity of 5-bromo- and 5-phenylterbenzimidazoles
AU Rangarajan, Meera; **Kim, Jung Sun**; Sim, Sai-Peng; Liu, Angela; **Liu, Leroy F.**; **LaVoie, Edmond J.**
CS Department of Pharmaceutical Chemistry, **Rutgers**, The State University of New Jersey, Piscataway, NJ, 08854, USA
SO Bioorganic & Medicinal Chemistry (2000), 8(11), 2591-2600
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 7, 28
OS CASREACT 134:95134
AB Topoisomerase I is an enzyme that is essential for maintaining the three-dimensional structure of DNA during the processes of transcription, translation and mitosis. With the introduction of new clin. agents that

are effective in poisoning topoisomerase I, this enzyme has proved to be an attractive mol. target in the development of anticancer drugs. Several terbenzimidazoles have been identified as potent topoisomerase I poisons. Structure-activity data on various terbenzimidazoles have revealed that the presence of lipophilic substituents at the 5-position of various terbenzimidazoles correlates with enhanced cytotoxicity. While the effect of having substituents at both the 5- and 6-positions had not been evaluated, previous studies did indicate that the presence of a fused benzo-ring at the 5,6-position results in a significant decrease in topoisomerase I poisoning activity and cytotoxicity. In the present study we investigated whether substituents at both the 5- and 6-positions of varied terbenzimidazoles would allow for retention of topo I poisoning activity. The 6-bromo, 6-methoxy, or 6-Ph derivs. of both 5-bromo- and 5-phenylterbenzimidazole were synthesized and evaluated for topo I poisoning activity, as well as their cytotoxicity toward human lymphoblastoma cells. The data indicate that such derivs. do retain similar topo I poisoning activity and possess cytotoxicity equivalent to either 5-bromo- or 5-phenylterbenzimidazole. Significant enhancement in the topoisomerase I poisoning activity and cytotoxicity of 5-phenylterbenzimidazole is observed when the 2"-position is substituted with either a chloro or trifluoromethyl substituent. The influence of such substituents on the biol. activity of 5,6-dibromoterbenzimidazole (I) was also explored. In the case of either 2"-chloro-5,6-dibromoterbenzimidazole or 2"-trifluoromethyl-5,6-dibromoterbenzimidazole (II), topoisomerase I poisoning was not enhanced relative to I. While cytotoxicity toward RPMI 8402 was also not significantly affected comparative studies performed against several solid human tumor cell lines did reveal a significant increase in cytotoxicity observed for II as compared to I.

ST terbenzimidazole prepn topoisomerase inhibition cytotoxicity structure

IT Antitumor agents
Structure-activity relationship
(synthesis, topoisomerase I inhibition and cytotoxicity of terbenzimidazoles)

IT **167959-27-5P 185199-36-4P 237429-45-7P**
237429-52-6P 237429-53-7P 237429-54-8P
237429-55-9P 237429-56-0P 237429-57-1P
237429-58-2P 237429-59-3P 288579-81-7P
319916-61-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis, topoisomerase I inhibition and cytotoxicity of terbenzimidazoles)

IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synthesis, topoisomerase I inhibition and cytotoxicity of terbenzimidazoles)

IT 875-51-4, 4-Bromo-2-nitroaniline 1679-18-1, p-Chlorophenylboronic acid 6943-69-7 17626-40-3 35998-98-2 75293-97-9, 3,4-Dibromo-6-nitroaniline 106429-45-2 106429-59-8 167959-20-8 288579-82-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis, topoisomerase I inhibition and cytotoxicity of terbenzimidazoles)

IT 1575-37-7P 31433-98-4P 49764-63-8P 108447-01-4P 117878-22-5P, [1,1':2',1''-Terphenyl]-4',5'-diamine 185199-45-5P 237429-70-8P
237429-71-9P 237429-73-1P 237429-74-2P 237429-75-3P 237429-76-4P
237429-77-5P 237429-78-6P 319916-62-6P 319916-63-7P 319916-64-8P
319916-65-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis, topoisomerase I inhibition and cytotoxicity of terbenzimidazoles)

RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
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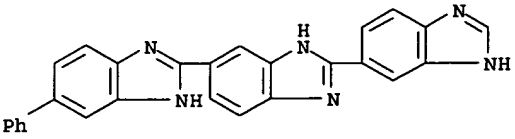
IT **167959-27-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis, topoisomerase I inhibition and cytotoxicity of terbenzimidazoles)

RN 167959-27-5 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole, 5-phenyl- (9CI) (CA INDEX NAME)



L25 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:454831 HCAPLUS
DN 133:171757
ED Entered STN: 06 Jul 2000
TI 2''-Substituted 5-phenylterbenzimidazoles as topoisomerase I poisons
AU Rangarajan, M.; **Kim, J. S.**; Jin, S.; Sim, S.-P.; Liu, A.; Pilch, D. S.; **Liu, L. F.**; **LaVoie, E. J.**
CS Department of Pharmaceutical Chemistry, **Rutgers**, The State University of New Jersey, Piscataway, NJ, 08854, USA
SO Bioorganic & Medicinal Chemistry (2000), 8(6), 1371-1382
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 28
AB 5-Phenylterbenzimidazole (1) is active as a topoisomerase I poison (topo I) and is cytotoxic to human tumor cells. No cross-resistance was observed for 1 when it was evaluated against the camptothecin-resistant cell line, CPT-K5. Derivs. of 1 substituted at the 2''-position, however, did exhibit cross-resistance to this cell line. The basis for the resistance of this cell line towards CPT is that it possesses a mutant form of topo I. These results suggest that substituents at the 2''-position may be in proximity to the wild-type enzyme. Therefore, we hypothesized that terbenzimidazoles with 2''-substituents could be capable of interacting with the enzyme and thereby influence activity within this class of topo I poisons. 5-Phenylterbenzimidazoles with a hydroxy, hydroxymethyl, mercapto, amino, N-benzoylaminomethyl, chloro, and trifluoromethyl group at the 2''-position were synthesized. In addition, several 2''-ethyl-5-phenylterbenzimidazoles were prepared containing either a methoxy, hydroxy, amino, or N-acetylamino group at the 2-position of the Et side-chain. These 2''-substituted 5-phenylterbenzimidazoles were evaluated as topo I poisons and for cytotoxic activity. The presence of a strong electron-withdrawing group at the 2''-position, such as a chloro or trifluoromethyl group, did enhance both topo I poisoning activity and cytotoxicity. Studies on the relative DNA binding affinity of 1 to its 2''-amino and 2''-trifluoromethyl derivs. did exhibit a correlation with their relative differences in biol. activity.
ST phenylterbenzimidazole deriv prepn antitumor topoisomerase inhibitor
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(binding; preparation of phenylterbenzimidazoles as topoisomerase I poisons)
IT Antitumor agents
Structure-activity relationship
(preparation of phenylterbenzimidazoles as topoisomerase I poisons)
IT **237429-44-6P 237429-45-7P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of phenylterbenzimidazoles as topoisomerase I poisons)
IT **167959-27-5**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(preparation of phenylterbenzimidazoles as topoisomerase I poisons)
IT **237429-50-4P 237429-51-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of phenylterbenzimidazoles as topoisomerase I poisons)
IT **192879-73-5P 192879-74-6P 192879-75-7P**
237429-42-4P 237429-43-5P 237429-46-8P
237429-47-9P 237429-48-0P 237429-49-1P
288579-81-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of phenylterbenzimidazoles as topoisomerase I poisons)
IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of phenylterbenzimidazoles as topoisomerase I poisons)
IT 57-13-6, Urea, reactions 76-05-1, Trifluoroacetic acid, reactions 79-14-1, reactions 107-95-9, .beta.-Alanine 140-89-6, Ethylxanthic acid potassium salt 495-69-2, Hippuric acid 506-68-3, Cyanogen bromide 4324-37-2, 2-Methoxypropionic acid 17626-40-3 35998-98-2, 3,4-Dinitrobenzaldehyde 192879-70-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of phenylterbenzimidazoles as topoisomerase I poisons)
IT 3671-61-2P 106429-45-2P 106429-59-8P 192879-72-4P 221289-88-9P 230308-95-9P 237429-60-6P 237429-61-7P 237429-62-8P 237429-63-9P 237429-64-0P 237429-65-1P 237429-66-2P 237429-67-3P 237429-68-4P 237429-69-5P 288579-82-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of phenylterbenzimidazoles as topoisomerase I poisons)
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
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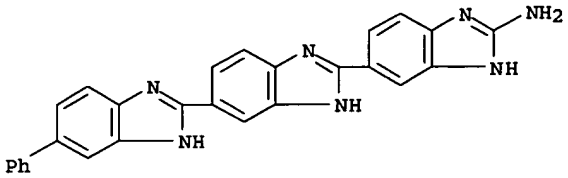
(36) Wells, R; J Mol Biol 1970, V54, P465 HCAPLUS
(37) Xu, Z; Biochemistry 1998, V37, P3558 HCAPLUS

IT **237429-44-6P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of phenylterbenzimidazoles as topoisomerase I poisons)
RN 237429-44-6 HCAPLUS
CN [2,5':2',5''-Ter-1H-benzimidazol]-2''-amine, 5-phenyl- (9CI) (CA INDEX NAME)



L25 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:269111 HCAPLUS
DN 133:53166
ED Entered STN: 26 Apr 2000
TI Heterocyclic bibenzimidazole derivatives as topoisomerase I inhibitors
AU Jin, Song; **Kim, Jung Sun**; Sim, Sai-Peng; Liu, Angela; Pilch, Daniel S.; **Liu, Leroy F.**; **LaVoie, Edmond J.**
CS Department of Pharmaceutical Chemistry, **Rutgers**, The State University of New Jersey, Piscataway, NJ, 08854-8020, USA
SO Bioorganic & Medicinal Chemistry Letters (2000), 10(8), 719-723
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 7, 28
AB A series of 2'-heterocyclic derivs. of 5-phenyl-2,5'-1H-bibenzimidazoles were evaluated for topoisomerase I poisoning activity and cytotoxicity. Topo I poisoning activity was associated with 2'-derivs. that possessed a hydrogen atom capable of hydrogen bond formation, suggesting that the interat. distances between such hydrogen atoms and the heteroatoms on the adjacent benzimidazole influence activity.
ST heterocyclic bibenzimidazole prepn topoisomerase I inhibitor
IT Molecular modeling
Structure-activity relationship
(preparation of heterocyclic bibenzimidazole derivs. as topoisomerase I inhibitors)
IT Cytotoxic agents
(preparation of heterocyclic bibenzimidazole derivs. as topoisomerase I inhibitors and cytotoxic agents)
IT Proliferation inhibition
(proliferation inhibitors; preparation of heterocyclic bibenzimidazole derivs. as topoisomerase I inhibitors and cytotoxic agents)
IT **167959-27-5P 230308-96-0P 230308-97-1P 230308-98-2P 277754-98-0P 277754-99-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclic bibenzimidazole derivs. as topoisomerase I inhibitors)
IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(preparation of heterocyclic bibenzimidazole derivs. as topoisomerase I inhibitors)

IT 1196-69-6, 5-Formylindole 1196-70-9, 6-Formylindole 230308-95-9 237429-60-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of heterocyclic bibenzimidazole derivs. as topoisomerase I inhibitors)

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(8) Pilch, D; Proc Natl Acad Sci USA 1997, V94, P13565 HCAPLUS
(9) Rangarajan, M; to be published in Bioorg Med Chem
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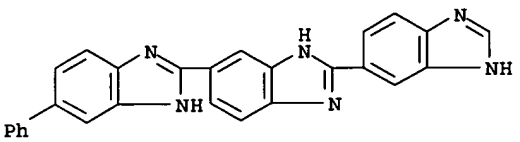
(11) Sun, Q; J Med Chem 1995, V38, P3638 HCAPLUS
(12) Xu, Z; Biochemistry 1998, V37, P3558 HCAPLUS

IT **167959-27-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclic bibenzimidazole derivs. as topoisomerase I inhibitors)

RN 167959-27-5 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole, 5-phenyl- (9CI) (CA INDEX NAME)



L25 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:529136 HCAPLUS
DN 131:157763
ED Entered STN: 24 Aug 1999
TI Preparation of terbenzimidazoles as topoisomerase I inhibitors
IN **Lavoie, Edmond J.**; **Kim, Jung Sun**; Rangarajan, Meera; **Liu, Leroy Fong**
PA **Rutgers**, the State University of New Jersey, USA
SO PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D235-18
ICS C07D235-26; C07D235-28; C07D235-30; A61K031-415; C07D491-04; C07D235-02; C07D491-04; C07D317-00; C07D235-00
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9941241	A1	19990819	WO 1999-US2966	19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6063801	A	20000516	US 1998-23147	19980212
CA 2318347	AA	19990819	CA 1999-2318347	19990212
AU 9926724	A1	19990830	AU 1999-26724	19990212
AU 748778	B2	20020613		
EP 1054870	A1	20001129	EP 1999-906928	19990212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

	IE, FI				
	JP 2002503653	T2	20020205	JP 2000-531436	19990212
	US 6221892	B1	20010424	US 2000-484402	20000114
	US 2001009919	A1	20010726	US 2001-796500	20010228
	US 6399642	B2	20020604		
PRAI	US 1998-23147	A2	19980212		
	WO 1999-US2966	W	19990212		
	US 2000-484402	A1	20000114		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9941241	ICM	C07D235-18
	ICS	C07D235-26; C07D235-28; C07D235-30; A61K031-415; C07D491-04; C07D235-02; C07D491-04; C07D317-00; C07D235-00
US 6063801	ECLA	C07D235/18; C07D235/26; C07D235/28; C07D235/30; C07D491/04+317A+235A
US 6221892	ECLA	C07D235/18; C07D235/26; C07D235/28; C07D235/30; C07D491/04+317A+235A
US 2001009919	ECLA	C07D235/18; C07D235/26; C07D235/28; C07D235/30; C07D491/04+317A+235A

OS MARPAT 131:157763

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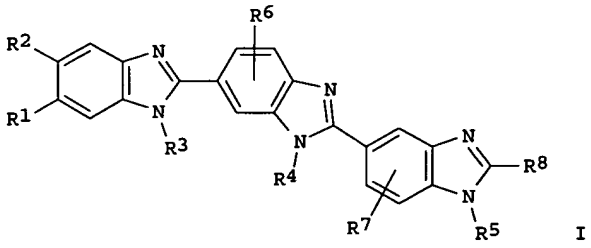


I

AB Title compds. [I; R1,R2 = H, halo, alkyl, alkoxy, etc.; R3-R5 = H, alkoxycarbonyl, (hetero)aryl(alkyl), etc.; R6,R7 = H, halo, alkyl, alkoxy, etc.; R8 = halo, (halo)alkyl, CO2H, etc.] were prepared Thus, 5-phenyl-2-(3,4-diaminophenyl)benzimidazole was cyclocondensed with 5-formyl-2-trifluoromethylbenzimidazole (preparation each given) to give I (R1,R3-R7 = H, R2 = Ph, R8 = CF3). Data for biol. activity of I were given.

ST terbenzimidazole prepn topoisomerase I inhibitor; antitumor terbenzimidazole prepn; antifungal terbenzimidazole prepn

IT Antitumor agents
Fungicides
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mediated disorders; treatment; preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT **167959-27-5P 185199-36-4P 192879-73-5P**
192879-74-6P 192879-75-7P 237429-42-4P
237429-43-5P 237429-44-6P 237429-45-7P
237429-46-8P 237429-47-9P 237429-48-0P
237429-49-1P 237429-50-4P 237429-51-5P
237429-52-6P 237429-53-7P 237429-54-8P
237429-55-9P 237429-56-0P 237429-57-1P
237429-58-2P 237429-59-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 98-80-6, Phenylboronic acid 107-95-9, .beta.-Alanine 495-69-2, Hippuric acid 591-19-5, 3-Bromoaniline 875-51-4, 4-Bromo-2-nitroaniline 2544-06-1, 3-Methoxypropionic acid 6393-40-4, 4-Amino-3-nitrobenzonitrile 6943-69-7 31433-98-4 35998-98-2, 3,4-Dinitrobenzaldehyde 167959-20-8 192879-70-2 192879-72-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 615-55-4P, 3,4-Dibromoaniline 1575-37-7P, 4-Bromo-1,2-diaminobenzene

3671-61-2P 17626-40-3P, 3,4-Diaminobenzonitrile 24108-97-2P, N-(3,4-Dibromophenyl)acetamide 49764-63-8P, 4,5-Dibromo-1,2-diaminobenzene 75293-96-8P 75293-97-9P, 3,4-Dibromo-6-nitroaniline 106429-45-2P 106429-59-8P 108447-01-4P 117878-22-5P, [1,1':2',1''-Terphenyl]-4',5'-diamine 185199-45-5P 221289-88-9P 230308-95-9P 237429-60-6P 237429-61-7P 237429-62-8P 237429-63-9P 237429-64-0P 237429-65-1P 237429-66-2P 237429-67-3P 237429-68-4P 237429-69-5P 237429-70-8P 237429-71-9P 237429-72-0P 237429-73-1P 237429-74-2P 237429-75-3P 237429-76-4P 237429-77-5P 237429-78-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

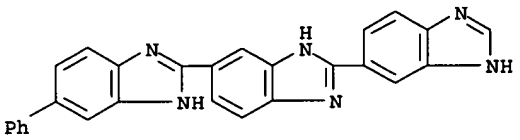
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Chen, A; Cancer Research 1993, V53(6), P1332 HCAPLUS
(2) Goldman, G; Biochemistry 1997, V36(21), P6488 HCAPLUS
(3) Kim, J; Journal of Medicinal Chemistry 1997, V40(18), P2818 HCAPLUS
(4) Pilch, D; Proceedings of the National Academy of Sciences of USA 1997, V94(2), P13565
(5) Rutgers, The State University of New Jersey; WO 9636612 A 1996 HCAPLUS
(6) Rutgers, The State University of New Jersey; WO 9831673 A 1998 HCAPLUS
(7) Sun, Q; Journal of Medicinal Chemistry 1995, V38(18), P3638 HCAPLUS

IT **167959-27-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

RN 167959-27-5 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole, 5-phenyl- (9CI) (CA INDEX NAME)



L25 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:460416 HCAPLUS
DN 131:87914
ED Entered STN: 28 Jul 1999
TI Heterocyclic topoisomerase poisons, namely 2-(benzimidazol-5-yl)benzimidazoles
IN **Lavoie, Edmond J.**; Kim, Jun Sung; **Liu, Leroy Fong**
PA **Rutgers**, the State University of New Jersey, USA
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D403-04
ICS A61K031-415
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9933824	A1	19990708	WO 1998-US27822	19981230
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2316221	AA	19990708	CA 1998-2316221	19981230
AU 9920220	A1	19990719	AU 1999-20220	19981230
AU 753268	B2	20021010		
EP 1044199	A1	20001018	EP 1998-965021	19981230
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002509858	T2	20020402	JP 2000-526506	19981230

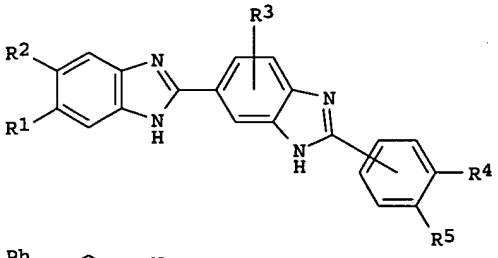
	US 2002151575	A1	20021017	US 2001-869141	20010613
	US 6667302	B2	20031223		
	US 2004082637	A1	20040429	US 2003-690800	20031021
PRAI	US 1997-70287P	P	19971231		
	WO 1998-US27822	W	19981230		
	US 2001-869141	A3	20010613		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9933824	ICM	C07D403-04
	ICS	A61K031-415
WO 9933824	ECLA	C07D235/20; C07D403/14+239+235C+235C; C07D403/14+249+235C+235C
US 2002151575	ECLA	C07D235/20; C07D403/14+239+235C+235C; C07D403/14+249+235C+235C
US 2004082637	ECLA	C07D235/20; C07D403/14+239+235C+235C; C07D403/14+249+235C+235C

OS MARPAT 131:87914

GI



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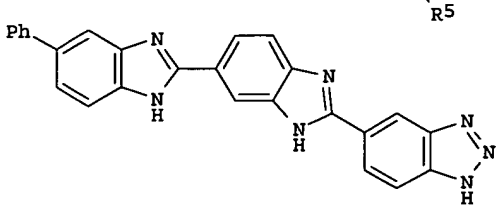


II

AB The invention provides title compds. I [R1, R2 = H, alkyl, cycloalkyl, alkoxy, (un)substituted (hetero)aryl, etc; or R1R2 = benzo, methylenedioxy; R3 = H, alkyl, cycloalkyl, alkoxy, OH, CF3O, halo, etc.; R4R5 = 3- to 5-atom ring-forming chain containing .gtoreq.1 NH group, and as further units O (except peroxides), S, N(X), C, or C(O), where X = null, H, O, alkyl, Ph, or PhCH2], as well as their pharmaceutically acceptable salts, pharmaceutical compns., and use of any of these to treat cancer. For instance, 5-phenyl-2-[2-(3,4-dinitrophenyl)benzimidazol-5-yl]benzimidazole was hydrogenated over Pd/C to give the 3,4-diamino compound, which underwent diazotization with concomitant cyclization to give title compound II. Two example compds. potently inhibited topoisomerase I in vitro, and also exhibited cytotoxic activity against RPMI 8402 cancer cells and camptothecin-resistant CPT-K5 cells in vitro.

ST heterocyclic topoisomerase poison benzimidazolylbenzimidazole prepn

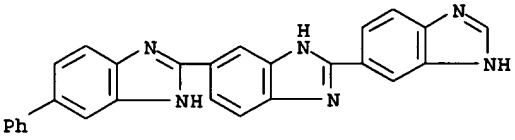
IT Antitumor agents
Cytotoxic agents
(preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)

IT Antitumor agents
(solid tumor, treatment; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)

IT **167959-27-5**, 5-Phenyl-2-[2-(benzimidazol-5-yl)benzimidazol-5-yl]benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparison compound; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)

IT 230308-98-2P, 5-Phenyl-2-[2-(quinoxalin-6-yl)benzimidazol-5-yl]benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(comparison compound; preparation of (benzimidazolyl)benzimidazoles as

topoisomerase poisons for use as anticancer agents)
IT 230308-95-9P, 5-Phenyl-2-[2-(3,4-diaminophenyl)benzimidazol-5-yl]benzimidazole
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
IT 144-62-7, Ethanedioic acid, reactions 517-21-5, Glyoxal disodium bisulfite 192879-72-4, 5-Phenyl-2-[2-(3,4-dinitrophenyl)benzimidazol-5-yl]benzimidazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
IT **230308-96-0P**, 5-Phenyl-2-[2-(1H-benzotriazol-5-yl)benzimidazol-5-yl]benzimidazole 230308-97-1P, 5-Phenyl-2-[2-(1,2,3,4-tetrahydro-2,3-dioxoquinoxalin-6-yl)benzimidazol-5-yl]benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(target compound; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Arznad; ARZNEIM-FORSCH 1974, V24(12), P1927
(2) Goldman, G; BIOCHEMISTRY 1997, V36(21), P6488 HCAPLUS
(3) Heinz, L; US 3538097 A 1970
(4) Kim, J; J MED CHEM 1996, V39(4), P992 HCAPLUS
(5) Kim, J; JOURNAL OF MEDICINAL CHEMISTRY 1997, V40(18), P2818 HCAPLUS
(6) Lavoie, E; WO 9636612 A 1996 HCAPLUS
(7) Lavoie, E; WO 9831673 A 1998 HCAPLUS
(8) Loewe, H; Basic substituted 2,6-bisbenzimidazole derivatives, a novel series of substances with chemotherapeutic activity 1975, 17, HCAPLUS
(9) Sun, Q; BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1994, V4(24), P2871 HCAPLUS
IT **167959-27-5**, 5-Phenyl-2-[2-(benzimidazol-5-yl)benzimidazol-5-yl]benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparison compound; preparation of (benzimidazolyl)benzimidazoles as topoisomerase poisons for use as anticancer agents)
RN 167959-27-5 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole, 5-phenyl- (9CI) (CA INDEX NAME)



L25 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:427779 HCAPLUS
DN 129:62952
ED Entered STN: 11 Jul 1998
TI Terbenzimidazoles useful as antifungal agents
IN **Lavoie, Edmond J.**; **Liu, Leroy Fong**; Sun, Qun
PA **Rutgers**, the State University of New Jersey, USA
SO U.S., 22 pp., Cont.-in-part of U.S. Ser. No. 618,988.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-415
NCL 514394000
CC 1-5 (Pharmacology)
Section cross-reference(s): 28
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI US 5770617 A 19980623 US 1997-786629 19970121
US 5767142 A 19980616 US 1996-618988 19960320
CA 2278452 AA 19980723 CA 1998-2278452 19980121
WO 9831673 A1 19980723 WO 1998-US1005 19980121
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9861327 A1 19980807 AU 1998-61327 19980121
AU 746663 B2 20020502
EP 960103 A1 19991201 EP 1998-905972 19980121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
BR 9806923 A 20000418 BR 1998-6923 19980121
NZ 336606 A 20010427 NZ 1998-336606 19980121
JP 2002513399 T2 20020508 JP 1998-534624 19980121
MX 9906793 A 20000228 MX 1999-6793 19990721
AU 9952697 A1 19991202 AU 1999-52697 19991005
AU 730456 B2 20010308
PRAI US 1996-618988 A2 19960320
AU 1996-57466 A3 19960514
US 1997-786629 A 19970121
WO 1998-US1005 W 19980121

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5770617	ICM	A61K031-415
	NCL	514394000
US 5767142	ECLA	C07D235/18; C07D401/14+235C+235C+235C+213; C07D401/14R+235C+213
WO 9831673	ECLA	C07D235/18; C07D401/14R+235C+213

OS MARPAT 129:62952
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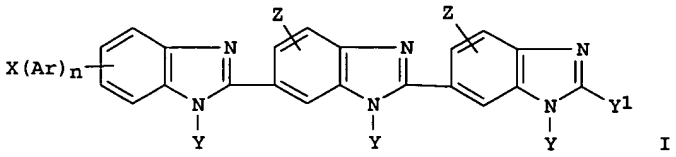


I

AB The present invention provides a method of treating fungal infection with an antifungal topoisomerase I inhibitor I [Ar = aryl, heteroaryl, benzo; X = H, CN, CHO, OH, acetyl, CF3, alkoxy, NO2, NH2, halogen, haloalkyl; Y = H, alkyl, aralkyl; Y1 = H, alkyl; n = 0, 1; Z = H, alkyl, halogen, haloalkyl] or their pharmaceutically acceptable salts. Thus, I [X = Y = Y1 = Z = H; Ar = Ph, n = 1, II] was obtained from 5-benimidazolecarboxylic acid and 4-phenyl-1,2-phenylenediamine in 4 steps. II is about one half as potent as Hoechst 33342 as a topoisomerase I inhibitor.

ST terbenzimidazole prepn topoisomerase I inhibitor fungicide

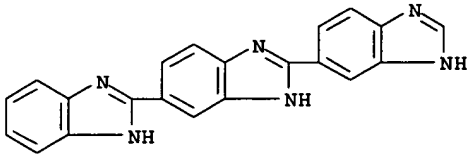
IT Fungicides
(terbenzimidazoles useful as antifungal agents)

IT **167959-21-9P**, 2,5':2',5''-Ter-1H-benzimidazole
167959-22-0P 167959-24-2P 167959-25-3P
167959-26-4P 167959-27-5P 185199-36-4P
185199-38-6P 185199-39-7P 209126-70-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(terbenzimidazoles useful as antifungal agents)

IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(terbenzimidazoles useful as antifungal agents)

IT 88-74-4, 2-Nitroaniline 106-39-8, 4-Bromo-1-chlorobenzene 1635-61-6, 5-Chloro-2-nitroaniline 6393-40-4, 4-Amino-3-nitrobenzonitrile 15788-16-6, 5-Benzimidazolecarboxylic acid 17626-40-3, 3,4-Diaminobenzonitrile 58442-17-4, 1H-Benzimidazole-5-carboxaldehyde

62579-61-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(terbenzimidazoles useful as antifungal agents)
IT 95-83-0P, 4-Chloro-1,2-phenylenediamine 875-51-4P, 4-Bromo-2-nitroaniline 1575-37-7P, 4-Bromo-1,2-phenylenediamine 4085-18-1P, 4-Phenyl-2-nitroaniline 17151-48-3P 59656-62-1P 160522-85-0P 167959-13-9P 167959-18-4P 167959-19-5P 167959-20-8P 185199-45-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(terbenzimidazoles useful as antifungal agents)
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Dykstra; US 5639755 1997 HCAPLUS
(2) Dykstra; US 5643935 1997 HCAPLUS
IT **167959-21-9P**, 2,5':2',5''-Ter-1H-benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(terbenzimidazoles useful as antifungal agents)
RN 167959-21-9 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole (9CI) (CA INDEX NAME)



L25 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:168435 HCAPLUS
DN 128:278724
ED Entered STN: 21 Mar 1998
TI Quantitative structure-activity relationships on 5-substituted terbenzimidazoles as topoisomerase I poisons and antitumor agents
AU **Kim, Jung Sun**; Sun, Qun; Yu, Chiang; Liu, Angela; **Liu, Leroy F.**; **Lavoie, Edmond J.**
CS Department of Pharmaceutical Chemistry, **Rutgers**, The State University of New Jersey, Piscataway, NJ, 08855, USA
SO Bioorganic & Medicinal Chemistry (1998), 6(2), 163-172
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 28
AB 5-Substituted terbenzimidazoles were synthesized and evaluated as mammalian topoisomerase I poisons and for cytotoxicity against a human lymphoblastoma cell line, RPMI-8402. No correlation was observed between topoisomerase I poisoning activity and the Hansch .pi. value or the .sigma.meta and .sigma.para values associated with each substituent. These data suggest that electronic effects and relative lipophilicity of substituents at the 5-position of these terbenzimidazoles do not have a significant effect upon intrinsic topoisomerase I poisoning activity. A good correlation between the relative .pi. values for the various substituents evaluated and cytotoxic activity was noted. Exptl. determined log P values did not correlate well with either cytotoxicity or .pi. values. Capacity factors (log k') as determined by high pressure liquid chromatog. did correlate well with the .pi. values of varied substituents and cytotoxicity. These data indicated that the relative lipophilic activity of substituents at the 5-position of these terbenzimidazoles can strongly influence relative cytotoxic activity.
ST terbenzimidazole topoisomerase I poisoning activity; cytotoxicity human lymphoblast cell; antitumor agent terbenzimidazole prepn; benzimidazole ter topoisomerase I poisoning activity
IT Antitumor agents
Cytotoxicity
QSAR (structure-activity relationship)
(QSAR on 5-substituted terbenzimidazoles as topoisomerase I poisons and antitumor agents)
IT **167959-21-9**, 2,5':2',5''-Ter-1H-benzimidazole **167959-22-0** **167959-23-1** **167959-27-5** **192879-67-7**

192879-68-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(QSAR on 5-substituted terbenzimidazoles as topoisomerase I poisons and antitumor agents)

IT 185199-36-4P 185199-38-6P 205749-93-5P
205749-94-6P 205749-95-7P 205749-96-8P
205749-97-9P, [2,5':2',5''-Ter-1H-benzimidazol]-5-ol
205749-98-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(QSAR on 5-substituted terbenzimidazoles as topoisomerase I poisons and antitumor agents)

IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(QSAR on 5-substituted terbenzimidazoles as topoisomerase I poisons and antitumor agents)

IT 96-96-8, 2-Nitro-4-methoxyaniline 99-56-9, 4-Nitrophenylene-1,2-diamine
364-78-3, 2-Nitro-4-fluoroaniline 875-51-4, 2-Nitro-4-bromoaniline
1635-61-6, 2-Nitro-5-chloroaniline 54997-99-8 167959-20-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(QSAR on 5-substituted terbenzimidazoles as topoisomerase I poisons and antitumor agents)

IT 95-83-0P 102-51-2P 367-31-7P 1575-37-7P 155198-10-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(QSAR on 5-substituted terbenzimidazoles as topoisomerase I poisons and antitumor agents)

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD

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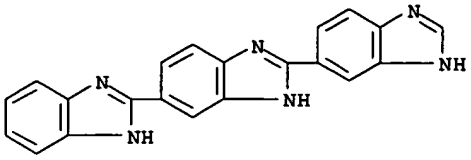
IT 167959-21-9, 2,5':2',5''-Ter-1H-benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(QSAR on 5-substituted terbenzimidazoles as topoisomerase I poisons and antitumor agents)

RN 167959-21-9 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole (9CI) (CA INDEX NAME)



L25 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:113031 HCAPLUS
DN 128:239061
ED Entered STN: 26 Feb 1998
TI DNA Minor Groove Binding-Directed Poisoning of Human DNA Topoisomerase I by Terbenzimidazoles
AU Xu, Zhitao; Li, Tsai-Kun; **Kim, Jung Sun**; **LaVoie, Edmond J.**; Breslauer, Kenneth J.; **Liu, Leroy F.**; Pilch, Daniel S.
CS Department of Pharmacology, University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School, Piscataway, NJ, 08854, USA
SO Biochemistry (1998), 37(10), 3558-3566
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 1-6 (Pharmacology)
AB We have employed a broad range of spectroscopic, calorimetric, DNA cleavage, and DNA winding/unwinding measurements to characterize the DNA binding and topoisomerase I (TOP1) poisoning properties of three terbenzimidazole analogs, 5-phenylterbenzimidazole (5PTB), terbenzimidazole (TB), and 5-(naphthyl[2,3-d]imidazo-2-yl)bibenzimidazole (5NIBB), which differ with respect to the substitutions at their C5 and/or C6 positions. Our results reveal the following significant features. (I) The overall extent to which the three terbenzimidazole analogs poison human TOP1 follows the hierarchy 5PTB > TB .mchgt. 5NIBB. (Ii) The impact of the three terbenzimidazole analogs on the superhelical state of plasmid DNA depends on the [total ligand] to [base pair] ratio (rbp), having no effect on DNA superhelicity at rbp ratios .ltoreq.0.1, while weakly unwinding DNA at rbp ratios >0.1. This weak DNA unwinding activity exhibited by the three terbenzimidazoles does not appear to be correlated with the abilities of these compds. to poison TOP1. (Iii) Upon complexation with both poly(dA).cntdot.poly(dT) and salmon testes DNA, the three terbenzimidazole analogs exhibit flow linear dichroism properties characteristic of a minor groove-directed mode of binding to these host DNA duplexes. (iv) The apparent minor groove binding affinities of the three terbenzimidazole analogs for the d(GA4T4C)2 duplex follow a qual. similar hierarchy to that noted above for ligand-induced poisoning of human TOP1-namely, 5PTB > TB > 5NIBB. In the aggregate, our results suggest that DNA minor groove binding, but not DNA unwinding, is important in the poisoning of TOP1 by terbenzimidazoles.
ST DAN topoisomerase I poison terbenzimidazole
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA minor groove binding in poisoning of topoisomerase I by terbenzimidazoles)
IT **167959-21-9**, Terbenzimidazole **167959-27-5** **192879-63-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(DNA minor groove binding in poisoning of topoisomerase I by terbenzimidazoles)
IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA minor groove binding in poisoning of topoisomerase I by terbenzimidazoles)
RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
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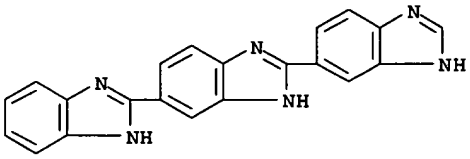
IT **167959-21-9**, Terbenzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(DNA minor groove binding in poisoning of topoisomerase I by terbenzimidazoles)

RN 167959-21-9 HCAPLUS

CN 2,5':2',5''-Ter-1H-benzimidazole (9CI) (CA INDEX NAME)



L25 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1997:802609 HCAPLUS

DN 128:123523

ED Entered STN: 25 Dec 1997

TI A terbenzimidazole that preferentially binds and conformationally alters structurally distinct DNA duplex domains: a potential mechanism for topoisomerase I poisoning

AU Pilch, Daniel S.; Xu, Zhitao; Sun, Qun; **LaVoie, Edmond J.**; **Liu, Leroy F.**; Breslauer, Kenneth J.

CS Dep. Pharmacol., Univ. Med. Dentistry New Jersey, Piscataway, NJ, 08854, USA

SO Proceedings of the National Academy of Sciences of the United States of America (1997), 94(25), 13565-13570
CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal

LA English

CC 1-6 (Pharmacology)

AB The terbenzimidazoles are a class of synthetic ligands that poison the

human topoisomerase I (TOP1) enzyme and promote cancer cell death. It has been proposed that drugs of this class act as TOP1 poisons by binding to the minor groove of the DNA substrate of TOP1 and altering its structure in a manner that results in enzyme-mediated DNA cleavage. To test this hypothesis, we characterize and compare the binding properties of a 5-phenylterbenzimidazole derivative (5PTB) to the d(GA4T4C)2 duplexes. The d(GA4T4C)2 duplex contains an uninterrupted 8-bp A.cntdot.T domain, which, on the basis of x-ray crystallog. data, should induce a highly hydrated "A-tract" conformation. This duplex also exhibits anomalously slow migration in a polyacrylamide gel, a feature characteristic of a noncanonical global conformational state frequently described as "bent." By contrast, the d(GT4A4C)2 duplex contains two 4-bp A.cntdot.T tracts separated by a TpA dinucleotide step, which should induce a less hydrated "B-like" conformation. This duplex also migrates normally in a polyacrylamide gel, a feature further characteristic of a global, canonical B-form duplex. Our data reveal that, at 20.degree., 5PTB exhibits an .apprxeq.2.3 kcal/mol greater affinity for the d(GA4T4C)2 duplex than for the d(GT4A4C)2 duplex. Significantly, we find this sequence/conformational binding specificity of 5PTB to be entropic in origin, an observation consistent with a greater degree of drug binding-induced dehydration of the more solvated d(GA4T4C)2 duplex. By contrast with the differential duplex affinity exhibited by 5PTB, netropsin and 4',6-diamindino-2-phenylindole (DAPI), two AT-specific minor groove binding ligands that are inactive as human TOP1 poisons, bind to both duplexes with similar affinities. The electrophoretic behaviors of the ligand-free and ligand-bound duplexes are consistent with 5PTB-induced bending and/or unwinding of both duplexes, which, for the d(GA4T4C)2 duplex, is synergistic with the endogenous sequence-directed electrophoretic properties of the ligand-free duplex state. By contrast, the binding to either duplex of netropsin or DAPI induces little or no change in the electrophoretic mobilities of the duplexes. Our results demonstrate that the TOP1 poison 5PTB binds differentially to and alters the structures of the two duplexes, in contrast to netropsin and DAPI, which bind with similar affinities to the two duplexes and do not significantly alter their structures. These results are consistent with a mechanism for TOP1 poisoning in which drugs such as 5PTB differentially target conformationally distinct DNA sites and induce structural changes that promote enzyme-mediated DNA cleavage.

ST topoisomerase I poison terbenzimidazole DNA conformation

IT Conformation
(B form; terbenzimidazole that preferentially binds and conformationally alters structurally distinct DNA duplex domains and potential mechanism for topoisomerase I poisoning)

IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cleavage; terbenzimidazole that preferentially binds and conformationally alters structurally distinct DNA duplex domains and potential mechanism for topoisomerase I poisoning)

IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(double-stranded; terbenzimidazole that preferentially binds and conformationally alters structurally distinct DNA duplex domains and potential mechanism for topoisomerase I poisoning)

IT Antitumor agents
Apoptosis
(terbenzimidazole that preferentially binds and conformationally alters structurally distinct DNA duplex domains and potential mechanism for topoisomerase I poisoning)

IT 122799-65-9
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(duplex; terbenzimidazole that preferentially binds and conformationally alters structurally distinct DNA duplex domains and potential mechanism for topoisomerase I poisoning)

IT 1438-30-8, Netropsin 47165-04-8, 4',6-Diamidino-2-phenylindole
167959-27-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(terbenzimidazole that preferentially binds and conformationally alters structurally distinct DNA duplex domains and potential mechanism for topoisomerase I poisoning)

IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(terbenzimidazole that preferentially binds and conformationally alters structurally distinct DNA duplex domains and potential mechanism for topoisomerase I poisoning)

RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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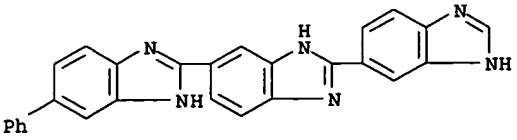
IT **167959-27-5**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(terbenzimidazole that preferentially binds and conformationally alters structurally distinct DNA duplex domains and potential mechanism for topoisomerase I poisoning)

RN 167959-27-5 HCAPLUS

CN 2,5':2',5''-Ter-1H-benzimidazole, 5-phenyl- (9CI) (CA INDEX NAME)



L25 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1997:526711 HCAPLUS

DN 127:117067

ED Entered STN: 18 Aug 1997

TI Terbenzimidazoles: Influence of 2''-, 4-, and 5-Substituents on Cytotoxicity and Relative Potency as Topoisomerase I Poisons

AU **Kim, Jung Sun**; Yu, Chiang; Liu, Angela; **Liu, Leroy F.**; **LaVoie, Edmond J.**
CS Department of Pharmaceutical Chemistry, **Rutgers** The State University of New Jersey, Piscataway, NJ, 08855, USA
SO Journal of Medicinal Chemistry (1997), 40(18), 2818-2824
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 28
AB Terbenzimidazoles poison the nuclear enzyme topoisomerase I and possess significant cytotoxic activity against several human tumor cell lines. The relative pharmacol. activity of 4,5- and 5,6-benzoterbenzimidazoles was compared to that of 5-phenylterbenzimidazole (3). 5,6-Benzoterbenzimidazole is inactive as a topoisomerase I poison and did not exhibit significant cytotoxic activity. In contrast, 4,5-benzoterbenzimidazole retained activity as a topoisomerase I poison but exhibited weak cytotoxic activity relative to 3. While 5-(1-naphthyl)terbenzimidazole is less potent than 3 as a topoisomerase I poison and cytotoxic agent, 5-(2-naphthyl)terbenzimidazole has comparable activity to 3. The presence of a p-methoxy or p-chloro substituent on the Ph moiety did not dramatically alter the pharmacol. activity of 3. Several analogs of 3 were synthesized wherein the 2''-substituent varied from Me, Et, Pr, iso-Pr, Ph to p-methoxyphenyl. Evaluation of the intrinsic activity of these analogs as topoisomerase I poisons indicates that topoisomerase I poisoning was not diminished by the presence of a Me, Et, Pr, and iso-Pr substituent at the 2''-position. Among the various 2''-substituted analogs evaluated, only in the case of 2''-(p-methoxyphenyl)-5-phenylterbenzimidazole was a significant decrease in cytotoxicity observed
ST terbenzimidazole prepn cytotoxicity topoisomerase DNA damage
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage; preparation, cytotoxicity and relative potency as topoisomerase I poisons of terbenzimidazoles)
IT Antitumor agents
Structure-activity relationship
(preparation, cytotoxicity and relative potency as topoisomerase I poisons of terbenzimidazoles)
IT **185199-39-7P 192879-62-2P 192879-63-3P 192879-64-4P 192879-67-7P 192879-68-8P 192879-69-9P 192879-73-5P 192879-74-6P 192879-75-7P 192879-76-8P 192879-77-9P 192879-78-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation, cytotoxicity and relative potency as topoisomerase I poisons of terbenzimidazoles)
IT 100-52-7, Benzaldehyde, biological studies **167959-27-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation, cytotoxicity and relative potency as topoisomerase I poisons of terbenzimidazoles)
IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation, cytotoxicity and relative potency as topoisomerase I poisons of terbenzimidazoles)
IT 75-07-0, Acetaldehyde, reactions 78-84-2, Isobutyraldehyde 90-11-9, 1-Bromonaphthalene 104-92-7, p-Bromoanisole 106-39-8, p-Bromochlorobenzene 123-11-5, p-Methoxybenzaldehyde, reactions 123-38-6, Propionaldehyde, reactions 123-72-8, Butyraldehyde 580-13-2, 2-Bromonaphthalene 771-97-1, 2,3-Naphthalenediamine 875-51-4 938-25-0, 1,2-Naphthalenediamine 972-09-8 972-11-2 4458-39-3, [1,1'-Biphenyl]-3,4-diamine 17151-48-3 35998-98-2 70744-47-7 102877-92-9, [1,1'-Biphenyl]-2,3-diamine 167959-20-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation, cytotoxicity and relative potency as topoisomerase I poisons of terbenzimidazoles)
IT 2221-02-5P 31433-98-4P 192879-65-5P 192879-66-6P 192879-70-2P 192879-72-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(preparation, cytotoxicity and relative potency as topoisomerase I poisons of terbenzimidazoles)
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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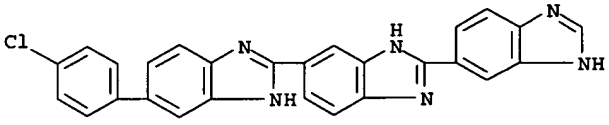
(24) Wang, J; Annu Rev Biochem 1996, V65, P635 HCAPLUS
IT **185199-39-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation, cytotoxicity and relative potency as topoisomerase I poisons of terbenzimidazoles)
RN 185199-39-7 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole, 5-(4-chlorophenyl)- (9CI) (CA INDEX NAME)



L25 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:299447 HCAPLUS
DN 126:340359
ED Entered STN: 10 May 1997
TI Differential Poisoning of Human and Aspergillus nidulans DNA Topoisomerase I by Bi- and Terbenzimidazoles
AU Goldman, Gustavo H.; Yu, Chiang; Wu, Hong-Yan; Sanders, Marilyn M.; La Voie, Edmond J.; **Liu, Leroy F.**
CS Department of Pharmacology Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, NJ, USA
SO Biochemistry (1997), 36(21), 6488-6494
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 7-3 (Enzymes)
Section cross-reference(s): 10
AB DNA topoisomerase I has been partially purified from Aspergillus nidulans. The purified enzyme is most likely the major nuclear DNA topoisomerase I on the basis of the following findings. (1) Purified DNA topoisomerase I can relax both pos. and neg. supercoiled DNA. (2) Neither an energy cofactor nor Mg(II) is required for the relaxation or the cleavage reaction of the enzyme. On the basis of a phosphate-transfer experiment, the Aspergillus topoisomerase I was shown to have a mol. mass (Mr) of 105 kDa. The differential sensitivity of the human and Aspergillus topoisomerase I was compared using a number of known human DNA topoisomerase I poisons. Like human DNA topoisomerase I, Aspergillus topoisomerase I is highly sensitive to the poisoning activity of camptothecin and a number of bi- and

terbenzimidazoles. However, unlike human topoisomerase I, Aspergillus topoisomerase I is completely resistant to monobenzimidazoles, protoberberines (e.g. coralyne), and nitidine. Cytotoxicity studies using yeast expressing human and yeast topoisomerase I cDNAs have also demonstrated a similar differential sensitivity of yeast topoisomerase I to these human topoisomerase I poisons. These results together suggest that the nuclear fungal topoisomerase I may be sufficiently different from its human counterpart to serve as a mol. target for the development of antifungal drugs.

ST Aspergillus human DNA topoisomerase inhibitor terbenzimidazole

IT Aspergillus nidulans
(differential poisoning of human and Aspergillus nidulans DNA topoisomerase I by bi- and terbenzimidazoles)

IT Structure-activity relationship
(enzyme-inhibiting, DNA topoisomerase I; differential poisoning of human and Aspergillus nidulans DNA topoisomerase I by bi- and terbenzimidazoles)

IT 143180-75-0P, DNA topoisomerase I
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(differential poisoning of human and Aspergillus nidulans DNA topoisomerase I by bi- and terbenzimidazoles)

IT 908-54-3, Berenil 6872-57-7, Nitidine 6872-73-7, Coralyne 7689-03-4, Camptothecin 23491-52-3, Hoechst 33342 91437-87-5 96954-35-7 113551-23-8 **167959-22-0 167959-27-5** 180077-27-4 189953-66-0
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(differential poisoning of human and Aspergillus nidulans DNA topoisomerase I by bi- and terbenzimidazoles)

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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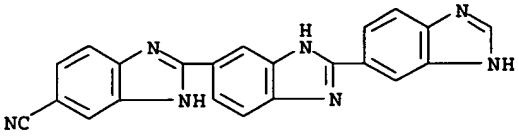
IT **167959-22-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)

(differential poisoning of human and Aspergillus nidulans DNA topoisomerase I by bi- and terbenzimidazoles)

RN 167959-22-0 HCAPLUS
CN [2,5':2',5''-Ter-1H-benzimidazole]-5-carbonitrile (9CI) (CA INDEX NAME)



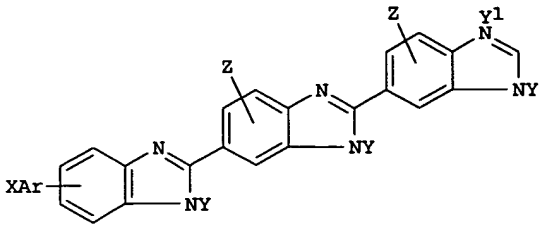
L25 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:41984 HCAPLUS
DN 126:59953
ED Entered STN: 20 Jan 1997
TI Preparation of tribenzimidazoles useful as topoisomerase I inhibitors.
IN **Lavoie, Edmond J.**; **Liu, Leroy Fong**; Sun, Qun
PA **Rutgers**, the State University of New Jersey, USA; Lavoie, Edmond J.; Liu, Leroy Fong; Sun, Qun
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D235-18
ICS A61K031-415; C07D401-14
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9636612	A1	19961121	WO 1996-US6853	19960514
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 5807874	A	19980915	US 1995-442657	19950517
US 5767142	A	19980616	US 1996-618988	19960320
CA 2221248	AA	19961121	CA 1996-2221248	19960514
AU 9657466	A1	19961129	AU 1996-57466	19960514
AU 713317	B2	19991125		
EP 839140	A1	19980506	EP 1996-915784	19960514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 11508229	T2	19990721	JP 1996-534375	19960514
BR 9608476	A	19990817	BR 1996-8476	19960514
US 5948797	A	19990907	US 1997-782064	19970113
AU 9952697	A1	19991202	AU 1999-52697	19991005
AU 730456	B2	20010308		
PRAI US 1995-442657	A	19950517		
US 1996-618988	A	19960320		
AU 1996-57466	A3	19960514		
WO 1996-US6853	W	19960514		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9636612	ICM	C07D235-18
	ICS	A61K031-415; C07D401-14
US 5807874	ECLA	C07D235/18; C07D401/14+235C+235C+235C+213
US 5767142	ECLA	C07D235/18; C07D401/14+235C+235C+235C+213; C07D401/14R+235C+213
US 5948797	ECLA	C07D235/18; C07D401/14+235C+235C+235C+213

OS MARPAT 126:59953
GI



I

AB Title compds. [I; Ar = 0-1 (substituted) aryl, heteroaryl which may be fused to the benzo moiety; X = H, CN, CHO, OH, Ac, CF3, alkoxy, NO2, NH2, halo, haloalkyl; Y = H, alkyl, aralkyl; Y1 = H, alkyl; ; Z = H, alkyl, halo, haloalkyl], were prepared Thus, 4-(4-pyridyl)-2-nitroaniline reacted with 5-formyl-2-(benzimidazol-5-yl)benzimidazole to give 43% 5-(4-pyridyl)-2-[2-(benzimidazol-5-yl)benzimidazol-5-yl]benzimidazole. This showed IC50 = 0.01 .mu.M against KBV-1 cells.

ST tribenzimidazole prepn topoisomerase inhibitor; anticancer tribenzimidazole prepn

IT Antitumor agents
(preparation of tribenzimidazoles useful as topoisomerase I inhibitors)

IT **167959-21-9P**, 2,5':2',5''-Ter-1H-benzimidazole
167959-22-0P 167959-23-1P 167959-24-2P
167959-25-3P 167959-26-4P 167959-27-5P
185199-36-4P 185199-38-6P 185199-39-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tribenzimidazoles useful as topoisomerase I inhibitors)

IT 143180-75-0
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of tribenzimidazoles useful as topoisomerase I inhibitors)

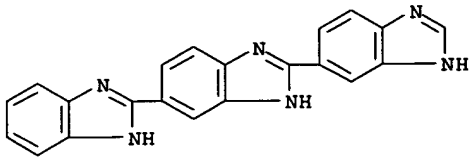
IT 88-74-4, 2-Nitroaniline 95-54-5, 1,2-Phenylenediamine, reactions 106-39-8, 4-Bromochlorobenzene 960-16-7, Phenyltributyltin 1635-61-6 15788-16-6, 5-Benzimidazolecarboxylic acid 17626-40-3 17997-47-6, 2-Tributylstannylpyridine 24850-33-7, Allyltributyltin 59020-10-9, 3-Tributylstannylpyridine 124252-41-1, 4-Tributylstannylpyridine
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tribenzimidazoles useful as topoisomerase I inhibitors)

IT 95-83-0P 875-51-4P 1575-37-7P 4085-18-1P 17151-48-3P 31433-98-4P 58442-17-4P, 1H-Benzimidazole-5-carboxaldehyde 59656-62-1P 160522-85-0P 167959-13-9P 167959-18-4P 167959-19-5P 167959-20-8P 185199-45-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tribenzimidazoles useful as topoisomerase I inhibitors)

IT **167959-21-9P**, 2,5':2',5''-Ter-1H-benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tribenzimidazoles useful as topoisomerase I inhibitors)

RN 167959-21-9 HCAPLUS

CN 2,5':2',5''-Ter-1H-benzimidazole (9CI) (CA INDEX NAME)



L25 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN

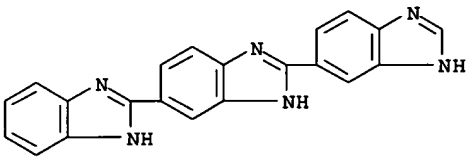
AN 1996:405834 HCAPLUS

DN 125:157872

ED Entered STN: 13 Jul 1996

TI Synthesis and structure-activity relationships of novel mammalian DNA topoisomerase I inhibitors (Hoechst dyes, terbenzimidazoles, antitumor

drugs)
AU Sun, Qun
CS **Rutgers**, State Univ., New Brunswick, NJ, USA
SO (1996) 173 pp. Avail.: Univ. Microfilms Int., Order No. DA9618556
From: Diss. Abstr. Int., B 1996, 57(2), 1093
DT Dissertation
LA English
CC 1-6 (Pharmacology)
AB Unavailable
ST DNA topoisomerase I inhibitor structure activity
IT Dyes
(Hoechst; synthesis and structure-activity relationships of novel mammalian DNA topoisomerase I inhibitors (Hoechst dyes, terbenzimidazoles, antitumor drugs))
IT Molecular structure-biological activity relationship
Neoplasm inhibitors
(synthesis and structure-activity relationships of novel mammalian DNA topoisomerase I inhibitors (Hoechst dyes, terbenzimidazoles, antitumor drugs))
IT **167959-21-9D**, 2,5':2',5''-Ter-1H-benzimidazole, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and structure-activity relationships of novel mammalian DNA topoisomerase I inhibitors (Hoechst dyes, terbenzimidazoles, antitumor drugs))
IT 143180-75-0, DNA topoisomerase I
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synthesis and structure-activity relationships of novel mammalian DNA topoisomerase I inhibitors (Hoechst dyes, terbenzimidazoles, antitumor drugs))
IT **167959-21-9D**, 2,5':2',5''-Ter-1H-benzimidazole, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and structure-activity relationships of novel mammalian DNA topoisomerase I inhibitors (Hoechst dyes, terbenzimidazoles, antitumor drugs))
RN 167959-21-9 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole (9CI) (CA INDEX NAME)



L25 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:746950 HCAPLUS
DN 123:198740
ED Entered STN: 19 Aug 1995
TI Synthesis and Evaluation of Terbenzimidazoles as Topoisomerase I Inhibitors
AU Sun, Qun; Gatto, Barbara; Yu, Chiang; Liu, Angela; **Liu, Leroy F.**; **LaVoie, Edmond J.**
CS Department of Pharmaceutical Chemistry, **Rutgers**, State University of New Jersey, Piscataway, NJ, 08855, USA
SO Journal of Medicinal Chemistry (1995), 38(18), 3638-44
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 28-18 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
OS CASREACT 123:198740
AB The synthesis and pharmacol. activity of a series of terbenzimidazoles are described. The ability of these derivs. to induce DNA cleavage in the presence of topoisomerase I was evaluated in vitro. These analogs were also assayed for their cytotoxicity in RPMI cells and the camptothecin-resistant CPT-K5 cells. In addition the potential for these

compds. to serve as substrates for MDR1 was also determined Several terbenzimidazoles exhibited similar cytotoxicity against variants of human tumor cells that either overexpress MDR1 or are camptothecin-resistant. Cyclocondensation of 1,2-benzenediamine with 2,5'-bi-1H-benzimdazole-5-carboxaldehyde gave 2,5':2',5''-Ter-1H-benzimidazole.

ST terbenzimidazole prepn topoisomerase inhibitor

IT 167959-13-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(2,5'-bi-1H-benzimdazole-5-carbonitrile; preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 167959-20-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(2,5'-bi-1H-benzimdazole-5-carboxaldehyde; preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT **167959-21-9P**, 2,5':2',5''-Ter-1H-benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(2,5':2',5''-Ter-1H-benzimidazole; preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 167959-14-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(2-(4-methoxyphenyl)-1H-Benzimidazole-5-carbonitrile; preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 167959-18-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(2-nitro-4-(2-pyridinyl)benzenamine; preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 167959-19-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(2-nitro-4-(3-pyridinyl)benzenamine; preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 143180-75-0
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 167959-15-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 23491-52-3DP, Hoechst 33342, analogs and derivs **167959-17-3P**
167959-22-0P 167959-23-1P 167959-24-2P
167959-25-3P 167959-26-4P 167959-27-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

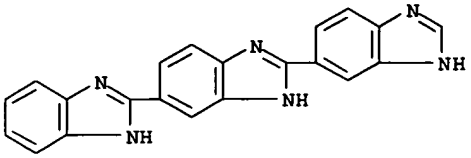
IT 88-74-4, Benzenamine, 2-nitro 95-54-5, 1,2-Benzenediamine, reactions 123-11-5, p-Anisaldehyde, reactions 960-16-7, Tributylphenyltin 6393-40-4, Benzonitrile, 4-amino-3-nitro 17626-40-3, Benzonitrile, 3,4-diamino 17997-47-6, 2-(Tributylstannyl)pyridine 24850-33-7, Allyltributyltin 59020-10-9, 3-(Tributylstannyl)pyridine 124252-41-1, 4-(Tributylstannyl)pyridine
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT 875-51-4P, Benzenamine, 4-bromo-2-nitro 4085-18-1P, [1,1'-Biphenyl]-4-amine, 3-nitro 58442-17-4P, 1H-Benzimidazole-5-carboxaldehyde 59656-62-1P, Benzenamine, 2-nitro-4-(4-pyridinyl) 126824-22-4P 160522-85-0P, Benzenamine, 2-nitro-4-(2-propenyl) 167959-16-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of terbenzimidazoles as topoisomerase I inhibitors)

IT **167959-21-9P**, 2,5':2',5''-Ter-1H-benzimidazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(2,5':2',5''-Ter-1H-benzimidazole; preparation of terbenzimidazoles as topoisomerase I inhibitors)

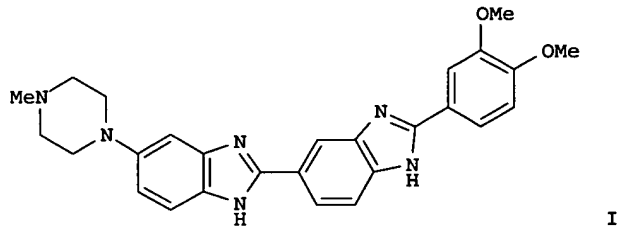
RN 167959-21-9 HCAPLUS

CN 2,5':2',5''-Ter-1H-benzimidazole (9CI) (CA INDEX NAME)



=> d all fhitstr l27 tot

L27 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:576172 HCAPLUS
DN 139:261219
ED Entered STN: 29 Jul 2003
TI Influence of Phenyl Ring Disubstitution on Bisbenzimidazole and Terbenzimidazole Cytotoxicity: Synthesis and Biological Evaluation as Radioprotectors
AU Tawar, Urmila; Jain, Akash K.; Dwarakanath, B. S.; Chandra, Ramesh; Singh, Yogendra; Chaudhury, N. K.; Khaitan, Divya; Tandon, Vibha
CS Dr. B. R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi, 110007, India
SO Journal of Medicinal Chemistry (2003), 46(18), 3785-3792
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
OS CASREACT 139:261219
GI



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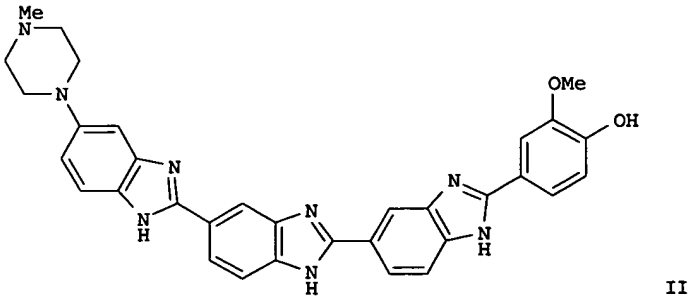

II

AB In a search of non-toxic and non-mutagenic DNA radioprotectors, two new disubstituted benzimidazoles I and II were synthesized. The radiomodifying effects of I and II were investigated with a human **glioma** cell line exposed to low linear energy transfer radiation by determining cell survival and cell **proliferation** compared with effects of the parent compound, Hoechst 33342. Cytotoxicity assayed by analyzing clonogenicity, cell growth, and metabolic viability showed that both I and II were non-toxic at 100 .mu.M after 72 h of exposure, whereas Hoechst 33342 resulted in lysis of 77% of these cells in 24 h. Macrocolony assay (clonogenicity) showed that 73%, 92%, and 10% of the cells survived when treated with 100 .mu.M I, II, and Hoechst 33342, resp. Both I and II did not affect the growth of BMG-1 cells. At 10 .mu.M, I

and II showed 82% and 37% protection against radiation-induced cell death (macrocolony assay) while 100% protection was observed against growth inhibition. Disubstitution of the Ph ring has not only reduced cytotoxicity but also enhanced DNA-ligand stability, conferring high degree of radioprotection.

ST benzimidazole bis disubstituted prepn cytotoxicity DNA binding radioprotective; terbenzimidazole disubstituted prepn cytotoxicity DNA binding radioprotective

IT Structure-activity relationship
(DNA-binding; preparation, cytotoxicity, DNA binding properties and radioprotective effects of piperazinyl bisbenzimidazole and terbenzimidazole)

IT Radiation
(damage; preparation, cytotoxicity, DNA binding properties and radioprotective effects of piperazinyl bisbenzimidazole and terbenzimidazole)

IT Cytotoxicity
Human
Radioprotectants
(preparation, cytotoxicity, DNA binding properties and radioprotective effects of piperazinyl bisbenzimidazole and terbenzimidazole)

IT 17626-40-3P, 3,4-Diaminobenzonitrile
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(heterocyclization with aldehyde; preparation, cytotoxicity, DNA binding properties and radioprotective effects of piperazinyl bisbenzimidazole and terbenzimidazole)

IT 120-14-9, 3,4-Dimethoxybenzaldehyde 121-33-5, 4-Hydroxy-3-methoxybenzaldehyde
RL: RCT (Reactant); RACT (Reactant or reagent)
(heterocyclization with diamine; preparation, cytotoxicity, DNA binding properties and radioprotective effects of piperazinyl bisbenzimidazole and terbenzimidazole)

IT 188860-26-6P **601473-44-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation, cytotoxicity, DNA binding properties and radioprotective effects of piperazinyl bisbenzimidazole and terbenzimidazole)

IT 23491-49-8P 601473-40-9P 601473-43-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, cytotoxicity, DNA binding properties and radioprotective effects of piperazinyl bisbenzimidazole and terbenzimidazole)

IT 6393-40-4, 4-Amino-3-nitrobenzonitrile 23623-05-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reduction; preparation, cytotoxicity, DNA binding properties and radioprotective effects of piperazinyl bisbenzimidazole and terbenzimidazole)

RE.CNT 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD

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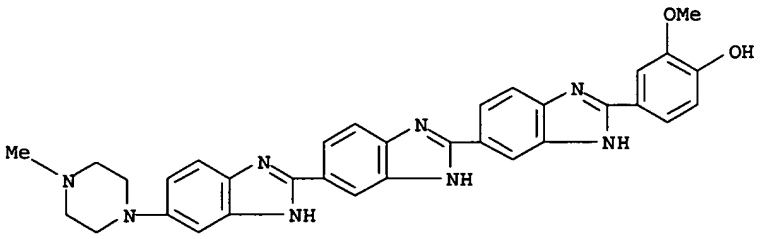
IT **601473-44-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation, cytotoxicity, DNA binding properties and radioprotective effects of piperazinyl bisbenzimidazole and terbenzimidazole)

RN 601473-44-3 HCAPLUS

CN Phenol, 2-methoxy-4-[5-(4-methyl-1-piperazinyl)[2,5':2',5''-ter-1H-benzimidazol]-2''-yl]- (9CI) (CA INDEX NAME)



L27 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:463129 HCAPLUS
DN 140:174411
ED Entered STN: 17 Jun 2003
TI Some new bi- and ter-benzimidazole derivatives as topoisomerase I inhibitors
AU Alper, Sabiha; Temiz Arpaci, Ozlem; Aki-Sener, Esin; Yalcin, Ismail
CS Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Ankara University Tandogan, Ankara, 06100, Turk.
SO Farmaco (2003), 58(7), 497-507
CODEN: FRMCE8; ISSN: 0014-827X
PB Editions Scientifiques et Medicales Elsevier
DT Journal
LA English
CC 1-3 (Pharmacology)
AB The discovery of DNA topoisomerases has added a new dimension to the study of anticancer drugs. In the last years detailed investigation

of bi- and ter-benzimidazole derivs. revealed that these compds. are a new class of topoisomerase I inhibitors that poisons mammalian topoisomerase I. In this context a survey about topoisomerase I poisoning activity and cytotoxicity of bi- and ter-benzimidazoles is given. Moreover some recent results about new derivs., some structure-activity relationships and comparison of activity of various functional groups are discussed.

ST topoisomerase I inhibitor benzimidazole deriv

IT **Antitumor** agents
Structure-activity relationship
(some new bi- and ter-benzimidazole derivs. as topoisomerase I inhibitors and **antitumor** activity)

IT 143180-75-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(some new bi- and ter-benzimidazole derivs. as topoisomerase I inhibitors and **antitumor** activity)

IT 2620-81-7 23491-54-5 23491-55-6 23554-98-5 23623-08-7 96954-35-7
96954-36-8 126824-21-3 126824-22-4 167959-13-9 167959-14-0
167959-15-1 **167959-17-3 167959-21-9**,
2,5':2',5''-Ter-1H-benzimidazole **167959-22-0 167959-23-1**
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167959-27-5 174422-17-4 174648-30-7 174648-31-8
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237429-59-3 277754-98-0 277754-99-1
319916-61-5
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(some new bi- and ter-benzimidazole derivs. as topoisomerase I inhibitors and **antitumor** activity)

RE.CNT 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD

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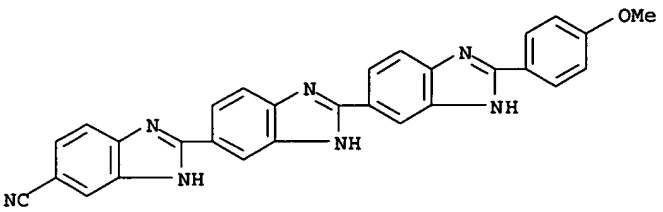
IT **167959-17-3**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(some new bi- and ter-benzimidazole derivs. as topoisomerase I inhibitors and **antitumor** activity)

RN 167959-17-3 HCAPLUS

CN [2,5':2',5''-Ter-1H-benzimidazole]-5-carbonitrile, 2''-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



L27 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:845775 HCAPLUS

DN 136:128592

ED Entered STN: 21 Nov 2001

TI Comparative QSAR studies on bibenzimidazoles and terbenzimidazoles inhibiting topoisomerase I

AU Mekapati, Suresh Babu; Hansch, Corwin

CS Department of Chemistry, Pomona College, Claremont, CA, 91711, USA

SO Bioorganic & Medicinal Chemistry (2001), 9(11), 2885-2893
CODEN: BMECEP; ISSN: 0968-0896

PB Elsevier Science Ltd.

DT Journal

LA English

CC 1-3 (Pharmacology)

AB Terbenzimidazoles that inhibit topoisomerase are of interest as **anticancer** drugs. We have reviewed the literature and have developed 13 quant. structure-activity relationships (QSARs) on cleaving DNA or inhibiting the growth of **tumor** cell cultures. The results are correlated with octanol/water partition coeffs. or mol. refractivity. Suggestions have been made for the development of improved derivs.

ST **antitumor** bisbenzimidazole terbenzimidazole QSAR topoisomerase I; **lymphoblastoma** bisbenzimidazole terbenzimidazole QSAR topoisomerase I

IT DNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cleavage; comparative QSAR studies on bisbenzimidazoles and terbenzimidazoles inhibiting topoisomerase I)

IT **Antitumor** agents
Human
Lymphoma
QSAR (structure-activity relationship)

(comparative QSAR studies on bisbenzimidazoles and terbenzimidazoles inhibiting topoisomerase I)
IT 143180-75-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(comparative QSAR studies on bisbenzimidazoles and terbenzimidazoles inhibiting topoisomerase I)
IT 2620-81-7 23491-52-3 23491-54-5 23491-55-6 23554-98-5 23623-06-5
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392287-19-3 392287-20-6 392287-21-7
392287-22-8 392287-23-9
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative QSAR studies on bisbenzimidazoles and terbenzimidazoles inhibiting topoisomerase I)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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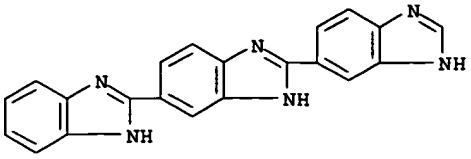
IT 167959-21-9, 2,5':2',5''-Ter-1H-benzimidazole
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative QSAR studies on bisbenzimidazoles and terbenzimidazoles inhibiting topoisomerase I)
RN 167959-21-9 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole (9CI) (CA INDEX NAME)



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L28 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:606451 HCAPLUS
DN 141:157115
ED Entered STN: 29 Jul 2004
TI A process for the synthesis of bisbenzimidazole derivatives, useful as radioprotective agents
IN Jain, Akash; Tawar, Urmila; Chandra, Ramesh; Dwarakanath, B. s.; Chaudhury, N. K.
PA University of Delhi, India; Tandon, Vibha
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D235-18
ICS C07D235-20
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 8
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004063170	A1	20040729	WO 2003-IN301	20030908

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI IN 2003-DE32 A 20030109
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004063170	ICM	C07D235-18
	ICS	C07D235-20

OS CASREACT 141:157115
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a preparation of bisbenzimidazole derivs., e.g. I, useful as radioprotective agents. The invented compds. are DNA binding ligands (Minor Groove Binding Ligands) that afford radioprotective effect without significant mutagenicity and cytotoxic effects. Cell survival assay showed that I has 73% cell survival at 100 .mu.M concentration For instance, I was prepared via heterocyclization of 3,4-dimethoxybenzaldehyde and benzimidazole derivative II with a yield of 30% (example 10).
ST bisbenzimidazole prepn radioprotectant radiation; dimethoxybenzaldehyde diamine heterocyclization
IT Heterocyclization
Human
Radioprotectants
(process for the synthesis of bisbenzimidazole derivs., useful as radioprotective agents)
IT Radiation
(treatment of; process for the synthesis of bisbenzimidazole derivs., useful as radioprotective agents)

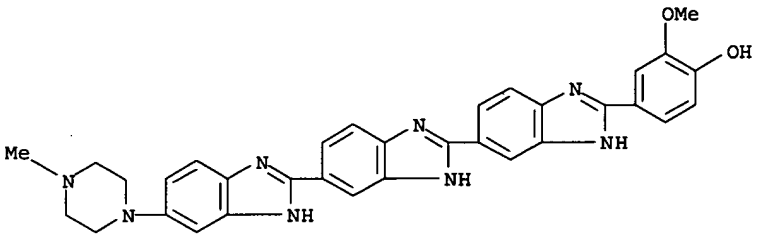
IT 188860-26-6P **601473-44-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the synthesis of bisbenzimidazole derivs., useful as radioprotective agents)

IT 109-01-3, 1-Methylpiperazine 121-33-5, 3-Methoxy-4-hydroxybenzaldehyde 588-07-8, m-Chloroacetanilide 5443-33-4 17626-40-3, 3,4-Diaminobenzonitrile 29289-18-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the synthesis of bisbenzimidazole derivs., useful as radioprotective agents)

IT 120-14-9P, 3,4-Dimethoxybenzaldehyde 1635-61-6P, 2-Nitro-5-chloroaniline 6393-40-4P 23491-48-7P 23491-49-8P 23623-05-4P 54998-08-2P 54998-39-9P 165596-29-2P 601473-40-9P 601473-43-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for the synthesis of bisbenzimidazole derivs., useful as radioprotective agents)

IT **601473-44-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the synthesis of bisbenzimidazole derivs., useful as radioprotective agents)

RN 601473-44-3 HCAPLUS
CN Phenol, 2-methoxy-4-[5-(4-methyl-1-piperazinyl)[2,5':2',5''-ter-1H-benzimidazol]-2''-yl]- (9CI) (CA INDEX NAME)



L28 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:877186 HCAPLUS
DN 140:93976
ED Entered STN: 10 Nov 2003
TI Synthesis of a terbenzimidazole topoisomerase I poison via iterative borinate ester couplings
AU Wang, Ben B.; Smith, Paul J.
CS Department of Chemistry and Biochemistry, University of Maryland, Baltimore, MD, 21250, USA
SO Tetrahedron Letters (2003), 44(50), 8967-8969
CODEN: TELEAY; ISSN: 0040-4039
PB Elsevier Science B.V.
DT Journal
LA English
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
AB A concise, efficient synthesis is described for a terbenzimidazole that acts as a potent topoisomerase I poison. The strategy involves iterative palladium-catalyzed borinate ester cross-couplings and should be applicable to the synthesis of analogs containing heterocycles other than benzimidazole.
ST terbenzimidazole topoisomerase poison coupling reaction borinate ester palladium catalyst
IT Cross-coupling reaction
Cross-coupling reaction catalysts
(preparation of terbenzimidazole topoisomerase I poison via iterative palladium-catalyzed cross-coupling reaction of corresponding borinate ester)

IT 14221-01-3, Tetrakis(triphenylphosphine)palladium 72287-26-4, Dichloro(diphenylphosphinoferrocene)palladium
RL: CAT (Catalyst use); USES (Uses)
(preparation of terbenzimidazole topoisomerase I poison via iterative palladium-catalyzed cross-coupling reaction of corresponding borinate ester)

IT 98-80-6, Phenylboronic acid 21304-38-1 73183-34-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of terbenzimidazole topoisomerase I poison via iterative palladium-catalyzed cross-coupling reaction of corresponding borinate ester)
IT 78597-27-0P 645414-73-9P 645414-74-0P 645414-75-1P 645414-76-2P 645414-77-3P 645414-78-4P 645414-79-5P **645414-80-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of terbenzimidazole topoisomerase I poison via iterative palladium-catalyzed cross-coupling reaction of corresponding borinate ester)
IT **167959-27-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of terbenzimidazole topoisomerase I poison via iterative palladium-catalyzed cross-coupling reaction of corresponding borinate ester)
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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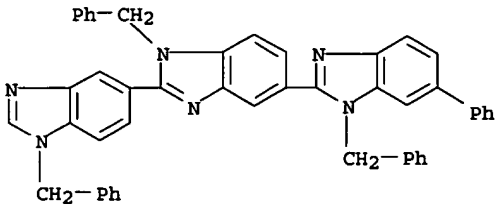
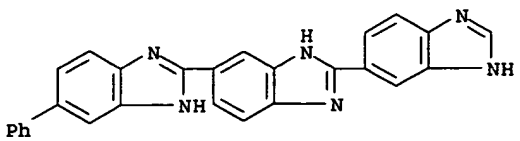
IT **645414-80-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of terbenzimidazole topoisomerase I poison via iterative palladium-catalyzed cross-coupling reaction of corresponding borinate ester)
RN 645414-80-8 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole, 6-phenyl-1,1',1''-tris(phenylmethyl)- (9CI) (CA INDEX NAME)



IT **167959-27-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of terbenzimidazole topoisomerase I poison via iterative palladium-catalyzed cross-coupling reaction of corresponding borinate ester)
RN 167959-27-5 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole, 5-phenyl- (9CI) (CA INDEX NAME)



L28 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:826193 HCAPLUS
DN 139:376009
ED Entered STN: 22 Oct 2003
TI Minor Groove Binding DNA Ligands with Expanded A/T Sequence Length Recognition, Selective Binding to Bent DNA Regions and Enhanced Fluorescent Properties
AU Tawar, Urmila; Jain, Akash K.; Chandra, Ramesh; Singh, Yogendra; Dwarakanath, B. S.; Chaudhury, N. K.; Good, Liam; Tandon, Vibha
CS Dr. B. R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi, 110007, India
SO Biochemistry (2003), 42(45), 13339-13346
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 3-3 (Biochemical Genetics)
AB DNA minor groove ligands provide a paradigm for double-stranded DNA recognition, where common structural motifs provide a crescent shape that matches the helix turn. Since minor groove ligands are useful in medicine, new ligands with improved binding properties based on the structural information about DNA-ligand complexes could be useful in developing new drugs. Here, two new synthetic analogs of AT specific Hoechst 33258 5-(4-methylpiperazin-1-yl)-2-[2'-(3,4-dimethoxyphenyl)-5'-benzimidazolyl] benzimidazole (DMA) and 5-(4-methylpiperazin-1-yl)-2-[2'{2''-(4-hydroxy-3-methoxyphenyl)-5''-benzimidazolyl}-5'-benzimidazolyl] benzimidazole (TBZ) were evaluated for their DNA binding properties. Both analogs are substituted on the Ph ring. DMA contains two ortho positioned methoxy groups, and TBZ contains a phenolic group at C-4 and a methoxy group at C-3. Fluorescence yield upon DNA binding increased 100-fold for TBZ and 16-fold for DMA. Like the parent compound, the new ligands showed low affinity to GC-rich (K .apprxeq. 4 .times. 107 M-1) relative to AT-rich sequences (K .apprxeq. 5 .times. 108 M-1), and fluorescence lifetime and anisotropy studies suggest two distinct DNA-ligand complexes. Binding studies indicate expanded sequence recognition for TBZ (8-10 AT base pairs) and tighter binding (.DELTA.Tm of 23 .degree.C for d (GA5T5C)). Finally, EMSA and equilibrium binding titration studies indicate that TBZ preferentially binds highly hydrated duplex domains with altered A-tract conformations d (GA4T4C)2 (K = 3.55 .times. 109 M-1) and alters its structure over d (GT4A4C)2 (K = 3.3 .times. 108 M-1) sequences. Altered DNA structure and higher fluorescence output for the bound fluorophore are consistent with adaptive binding and a constrained final complex. Therefore, the new ligands provide increased sequence and structure selective recognition and enhanced fluorescence upon minor groove binding, features that can be useful for further development as probes for chromatin structure stability.
ST DNA ligand AT minor groove helix conformation fluorescence
IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AT-rich element; minor groove-binding DNA ligands recognizes AT-rich sequence and enhances fluorescence)
IT Conformation
Helix (conformation)
(DNA; minor groove-binding DNA ligands recognizes AT-rich sequence and enhances fluorescence)
IT Fluorescence
(minor groove-binding DNA ligands recognizes AT-rich sequence and enhances fluorescence)
IT DNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(minor groove-binding DNA ligands recognizes AT-rich sequence and enhances fluorescence)
IT 188860-26-6 **601473-44-3**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(minor groove-binding DNA ligands recognizes AT-rich sequence and enhances fluorescence)
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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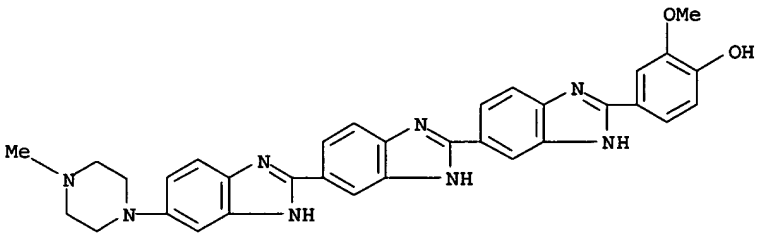
IT **601473-44-3**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(minor groove-binding DNA ligands recognizes AT-rich sequence and enhances fluorescence)

RN 601473-44-3 HCAPLUS

CN Phenol, 2-methoxy-4-[5-(4-methyl-1-piperazinyl)[2,5':2',5''-ter-1H-benzimidazol]-2''-yl]- (9CI) (CA INDEX NAME)



L28 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:845778 HCAPLUS
DN 136:131135
ED Entered STN: 21 Nov 2001
TI Tris-benzimidazole derivatives: design, synthesis and DNA sequence recognition
AU Ji, Yu-Hua; Bur, Daniel; Hasler, Walter; Schmitt, Valerie Runtz; Dorn, Arnulf; Bailly, Christian; Waring, Michael J.; Hochstrasser, Remo; Leupin, Werner
CS Pharma Research Preclinical Gene Technologies and Infectious Diseases, F. Hoffmann-La Roche Ltd, Basel, CH-4070, Switz.
SO Bioorganic & Medicinal Chemistry (2001), 9(11), 2905-2919
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
CC 9-14 (Biochemical Methods)
AB Two tris-benzimidazole derivs. have been designed and synthesized based on the known structures of the bis-benzimidazole stain Hoechst 33258 complexed to short oligonucleotide duplexes derived from single crystal x-ray studies and from NMR. In both derivs. the phenol group has been replaced by a methoxy-Ph substituent. Whereas one tris-benzimidazole carries a N-methyl-piperazine at the 6-position, the other one has this group replaced by a 2-amino-pyrrolidine ring. This latter substituent

results in stronger DNA binding. The optimized synthesis of the drugs is described. The two tris-benzimidazoles exhibit high AT-base pair (bp) selectivity evident in footprinting expts. which show that five to six base pairs are protected by the tris-benzimidazoles as compared to four to five protected by the bis-benzimidazoles. The tris-benzimidazoles bind well to sequences like 5'-TAAAC, 5'-TTTAC and 5'-TTTAT, but it is also evident that they can bind weakly to sequences such as 5'-TATGTT-3' where the continuity of an AT stretch is interrupted by a single G.cntdot.C base pair.

ST benzimidazole deriv prepn DNA sequence recognition; DNase footprinting benzimidazole deriv prepn

IT DNA sequences
(design, synthesis and DNA sequence recognition using tris-benzimidazole derivs.)

IT 98-95-3, Nitrobenzene, reactions 109-01-3, N-Methylpiperazine 123-11-5, 4-Methoxybenzaldehyde, reactions 528-45-0, 3,4-Dinitrobenzoic acid 5344-44-5, 5-Chloro-3-nitroaniline 16645-06-0, Dimethylhydroxylamine hydrochloride 37466-90-3 99724-19-3, 3-tert-Butoxycarbonylaminopyrrolidine
RL: RCT (Reactant); RACT (Reactant or reagent)
(design, synthesis and DNA sequence recognition using tris-benzimidazole derivs.)

IT 24376-18-9P 126824-19-9P 126824-21-3P 126824-22-4P 167959-16-2P 391903-19-8P 391903-20-1P 391903-21-2P 391903-22-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis and DNA sequence recognition using tris-benzimidazole derivs.)

IT 23491-48-7P **182496-21-5P** 391903-23-4P 391903-24-5P **391903-25-6P** 391903-26-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(design, synthesis and DNA sequence recognition using tris-benzimidazole derivs.)

IT 9003-98-9, DNase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(footprinting; design, synthesis and DNA sequence recognition using tris-benzimidazole derivs.)

RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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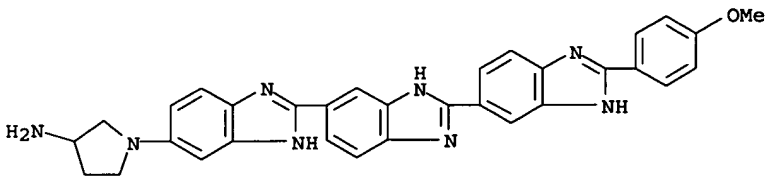
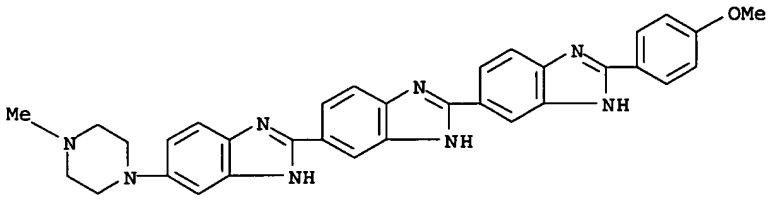
IT **182496-21-5P 391903-25-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(design, synthesis and DNA sequence recognition using tris-benzimidazole derivs.)

RN 182496-21-5 HCAPLUS
CN 3-Pyrrolidinamine, 1-[2''-(4-methoxyphenyl)[2,5':2',5''-ter-1H-benzimidazol]-5-yl]- (9CI) (CA INDEX NAME)



RN 391903-25-6 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole, 2''-(4-methoxyphenyl)-5-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



L28 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:656650 HCAPLUS
DN 135:368118
ED Entered STN: 07 Sep 2001
TI Molecular modelling of ligand-DNA minor groove binding: role of ligand-water interactions
AU Mikheikin, A. L.; Zhuze, A. L.; Zasedatelev, A. S.
CS Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, 119991, Russia
SO Journal of Biomolecular Structure & Dynamics (2001), 19(1), 175-178
CODEN: JBSDD6; ISSN: 0739-1102
PB Adenine Press
DT Journal
LA English
CC 6-2 (General Biochemistry)
AB A procedure was developed for quant. estimation of the ligand affinity for the DNA minor groove with allowance for ligand hydration, whereby the binding energy was calculated as the difference in the energies of ligand-DNA and ligand-water interactions. Adequacy of the procedure was demonstrated with the structural motifs (pyrrolecarboxamide, benzimidazole, furancarboxamide, and phthalimide) of well-known ligands for the case of a d(GCA10CG).cntdot.d(CGT10GC) duplex. On the strength of the results

obtained, an indole-based motif was proposed as the basis for a highly affined minor groove binder.
ST DNA minor groove interaction ligand
IT Hydration, chemical
(hydration and hydrophobic interactions in ligand-DNA complexes also play role in binding of ligand to DNA minor groove)
IT Molecular association
(mol. modeling of ligand-DNA minor groove binding and role of ligand-water interactions)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(mol. modeling of ligand-DNA minor groove binding and role of ligand-water interactions)
IT 7732-18-5, Water, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mol. modeling of ligand-DNA minor groove binding and role of ligand-water interactions)
IT 636-47-5, Distamycin A 23491-45-4, Hoechst 33258 47165-04-8, DAPI
168100-52-5 373596-17-9 373596-18-0 **373596-19-1**
373596-20-4 373596-21-5 373596-22-6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mol. modeling of ligand-DNA minor groove binding and role of ligand-water interactions)
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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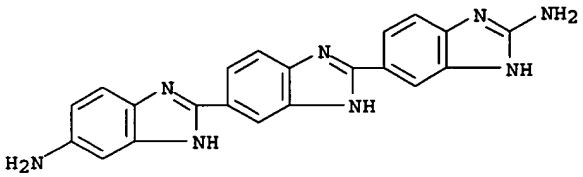
IT **373596-19-1**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mol. modeling of ligand-DNA minor groove binding and role of ligand-water interactions)
RN 373596-19-1 HCAPLUS
CN [2,5':2',5''-Ter-1H-benzimidazole]-2'',5-diamine (9CI) (CA INDEX NAME)



L28 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:748488 HCAPLUS
DN 134:291615
ED Entered STN: 24 Oct 2000
TI Molecular recognition of DNA by Hoechst benzimidazoles: exploring beyond the pyrrole-imidazole-hydroxypyrrole polyamide-pairing code
AU Minehan, Thomas G.; Gottwald, Konstanze; Dervan, Peter B.
CS Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA
SO Helvetica Chimica Acta (2000), 83(9), 2197-2213
CODEN: HCACAV; ISSN: 0018-019X
PB Verlag Helvetica Chimica Acta
DT Journal
LA English
CC 6-2 (General Biochemistry)
Section cross-reference(s): 28
OS CASREACT 134:291615
AB A series of three-ring analogs of the minor-groove-binding mol. Hoechst 33258 (1), consisting of benzimidazole (B), imidazopyridine (P), and hydroxybenzimidazole (H) monomers, have been synthesized in order to

investigate both their sequence specificity and binding modes. MPE.cntdot.FeII Footprinting has revealed the preference of both PBB and BBB ligands for 5'-WGWWW-3' and 5'-WCWWW-3' tracts, as well as A.cntdot.T-rich sequences. Affinity-cleavage titrns. show no evidence for a 2:1 binding mode of these Hoechst analogs. Importantly, all derivs. are oriented in one direction at each of their binding sites. The implications of these results for the design of minor-groove-binding small mols. is discussed.

ST DNA recognition Hoechst 33258 benzimidazole analog prepn

IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(double-stranded; preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

IT Molecular orientation
(in minor-groove; preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

IT Molecular recognition
(preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

IT 23491-45-4, Hoechst 33258 334685-20-0 334685-35-7
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

IT **334685-29-9P** 334685-30-2P **334685-33-5P** 334685-34-6P
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

IT 105-36-2, Ethyl bromoacetate 105-83-9, Bis(3-aminopropyl)methylamine 109-55-7, 3-(Dimethylamino)propylamine 110-85-0, Piperazine, reactions 1635-61-6, 5-Chloro-2-nitroaniline 6291-84-5, (3-Aminopropyl)methylamine 23911-25-3, EDTA dianhydride 126463-85-2 126824-22-4 142764-79-2 183296-71-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

IT 96103-52-5P 126436-26-8P 126463-87-4P **167959-17-3P** 188247-41-8P 188247-43-0P 334685-22-2P 334685-25-5P **334685-27-7P** **334685-31-3P** 334685-32-4P 416850-41-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

IT **334685-21-1P** 334685-28-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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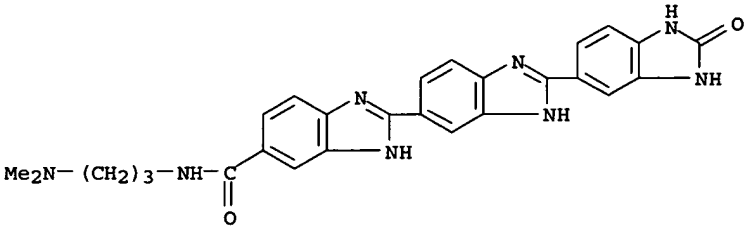
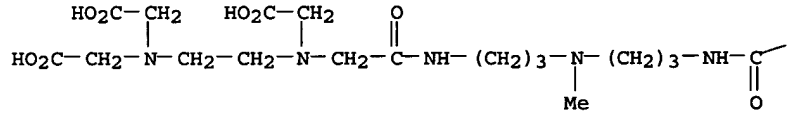
IT **334685-29-9P 334685-33-5P**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

RN 334685-29-9 HCAPLUS
CN [2,5':2',5''-Ter-1H-benzimidazole]-5-carboxamide, N-[3-(dimethylamino)propyl]-2'',3''-dihydro-2''-oxo- (9CI) (CA INDEX NAME)

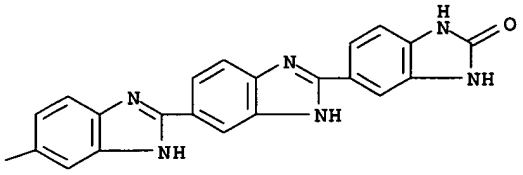


RN 334685-33-5 HCAPLUS
CN 2,6,10,13,16-Pentaazaoctadecan-18-oic acid, 13,16-bis(carboxymethyl)-1-(2'',3''-dihydro-2''-oxo[2,5':2',5''-ter-1H-benzimidazol]-5-yl)-6-methyl-1,11-dioxo- (9CI) (CA INDEX NAME)

PAGE 1-A

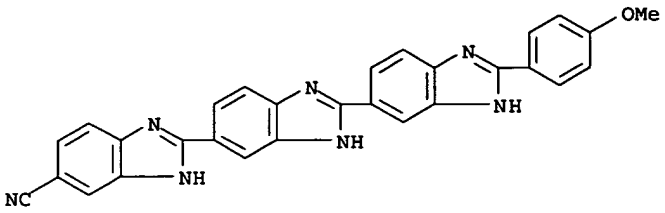


PAGE 1-B

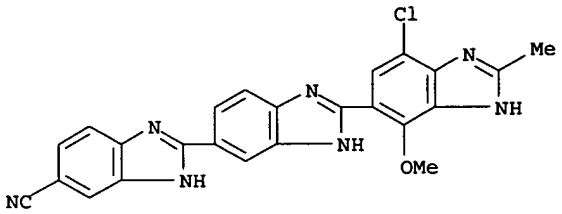


IT **167959-17-3P 334685-27-7P 334685-31-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)

RN 167959-17-3 HCAPLUS
CN [2,5':2',5''-Ter-1H-benzimidazole]-5-carbonitrile, 2''-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)

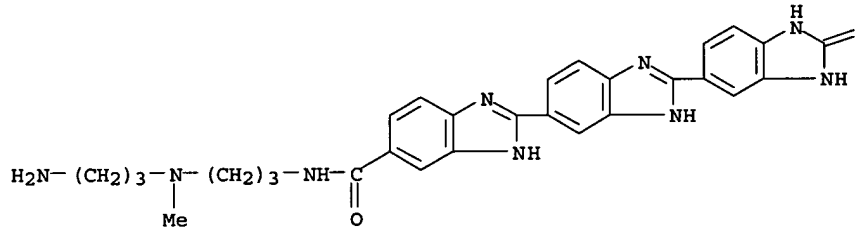


RN 334685-27-7 HCAPLUS
CN [2,5':2',5''-Ter-1H-benzimidazole]-5-carbonitrile, 7''-chloro-4''-methoxy-2''-methyl- (9CI) (CA INDEX NAME)



RN 334685-31-3 HCAPLUS
CN [2,5':2',5''-Ter-1H-benzimidazole]-5-carboxamide, N-[3-[(3-aminopropyl)methylamino]propyl]-2'',3''-dihydro-2''-oxo- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

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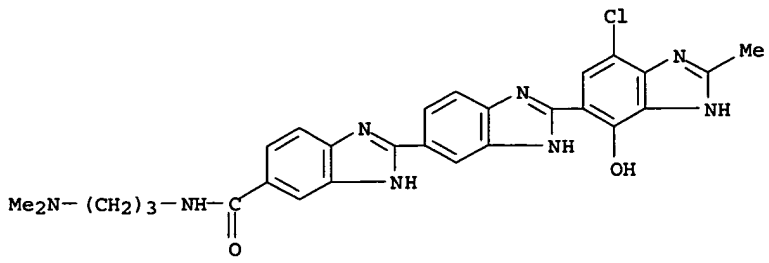
IT **334685-21-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and mol. recognition of DNA minor groove by Hoechst 33258 benzimidazole analogs)
RN 334685-21-1 HCAPLUS
CN [2,5':2',5''-Ter-1H-benzimidazole]-5-carboxamide, 7''-chloro-N-[3-(dimethylamino)propyl]-4''-hydroxy-2''-methyl- (9CI) (CA INDEX NAME)



L28 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:124956 HCAPLUS
DN 132:274285
ED Entered STN: 24 Feb 2000
TI The interaction of benzimidazole compounds with DNA: intercalation and groove binding modes
AU Kubota, Yukio; Iwamoto, Takayuki; Seki, Toshimasa
CS Department of Chemistry, Faculty of Science, Yamaguchi University, Yamaguchi, 753-8512, Japan
SO Nucleic Acids Symposium Series (1999), 42(Twentysixth Symposium on Nucleic Acids Chemistry, 1999), 53-54
CODEN: NACSD8; ISSN: 0261-3166
PB Oxford University Press
DT Journal
LA English
CC 1-12 (Pharmacology)
AB Benzimidazole compds. have been synthesized to study their DNA-binding properties. Results obtained with spectroscopy and viscosity measurements indicate that the binding mode varies from intercalation to groove-binding, depending on the number of benzimidazole rings (conformation and size of compds.).
ST benzimidazole intercalation DNA intercalation
IT Conformation
Molecular association
(interaction of benzimidazole compds. with DNA in relation to intercalation and groove binding modes and conformation)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interaction of benzimidazole compds. with DNA in relation to intercalation and groove binding modes and conformation)
IT Intercalation
(nucleic acid; interaction of benzimidazole compds. with DNA in relation to intercalation and groove binding modes and conformation)
IT 154713-23-2 263707-95-5 **263707-96-6 263707-97-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(interaction of benzimidazole compds. with DNA in relation to intercalation and groove binding modes and conformation)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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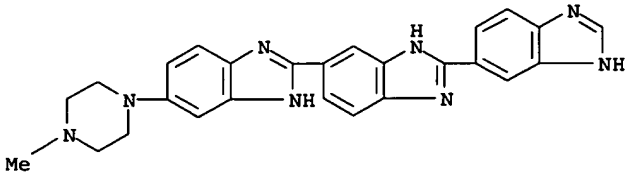
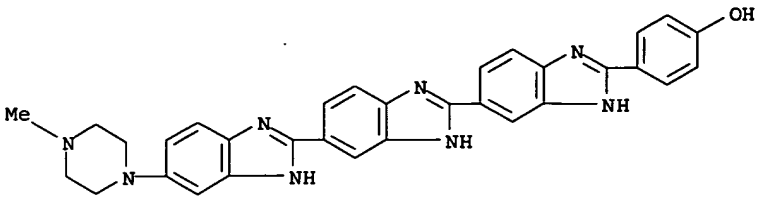
IT **263707-96-6 263707-97-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(interaction of benzimidazole compds. with DNA in relation to intercalation and groove binding modes and conformation)
RN 263707-96-6 HCAPLUS
CN 2,5':2',5''-Ter-1H-benzimidazole, 5-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



RN 263707-97-7 HCAPLUS
CN Phenol, 4-[5-(4-methyl-1-piperazinyl)[2,5':2',5''-ter-1H-benzimidazol]-2''-yl]- (9CI) (CA INDEX NAME)



L28 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:446949 HCAPLUS
DN 132:60607
ED Entered STN: 21 Jul 1999
TI DNA minor groove recognition of a non-self-complementary AT-rich sequence by a tris-benzimidazole ligand
AU Aymami, Juan; Nunn, Christine M.; Neidle, Stephen
CS CRC Biomolecular Structure Unit, Institute of Cancer Research, Surrey, SM2 5NG, UK
SO Nucleic Acids Research (1999), 27(13), 2691-2698
CODEN: NARHAD; ISSN: 0305-1048
PB Oxford University Press
DT Journal
LA English
CC 6-2 (General Biochemistry)
Section cross-reference(s): 1, 75
AB The crystal structure of the non-self-complementary dodecamer DNA duplex formed by d(CG[5BrC]ATATTTGCG) and d(CGCAAATATGCG) has been solved to 2.3 .ANG. resolution, together with that of its complex with the tris-benzimidazole minor groove binding ligand TRIBIZ. The inclusion of a bromine atom on one strand in each structure enabled the possibility of disorder to be discounted. The native structure has an exceptional narrow minor groove, of 2.5-2.6 .ANG. in the central part of the A/T region, which is increased in width by .apprx.0.8 .ANG. on drug binding. The ligand mol. binds in the central part of the sequence. The benzimidazole subunits of the ligand participate in six bifurcated hydrogen bonds with A:T base pair edges, three to each DNA strand. The presence of a pair of C-H...O hydrogen bonds has been deduced from the close proximity of the pyrrolidine group of the ligand to the TpA step in the sequence.
ST DNA TRIBIZ structure recognition
IT Crystal structure
Molecular recognition
(DNA minor groove recognition of non-self-complementary AT-rich sequence by tris-benzimidazole ligand)
IT Conformation
(DNA; DNA minor groove recognition of non-self-complementary AT-rich sequence by tris-benzimidazole ligand)
IT Molecular structure
(cDNA minor groove recognition of non-self-complementary AT-rich sequence by tris-benzimidazole ligand)
IT **182496-21-5**, TRIBIZ 253331-47-4
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(DNA minor groove recognition of non-self-complementary AT-rich sequence by tris-benzimidazole ligand)
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Abu-Daya, A; Nucleic Acids Res 1995, V23, P3385 HCAPLUS
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(5) Chen, X; J Mol Biol 1997, V267, P1157 HCAPLUS
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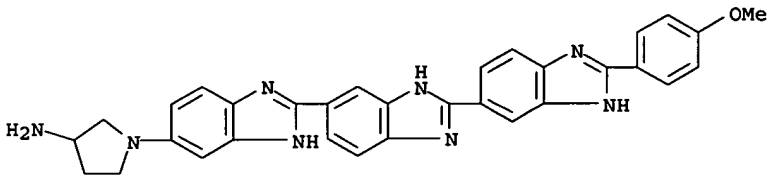
IT **182496-21-5**, TRIBIZ
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(DNA minor groove recognition of non-self-complementary AT-rich sequence by tris-benzimidazole ligand)

RN 182496-21-5 HCAPLUS

CN 3-Pyrrolidinamine, 1-[2''-(4-methoxyphenyl)[2,5':2',5''-ter-1H-benzimidazol]-5-yl]- (9CI) (CA INDEX NAME)



L28 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:523091 HCAPLUS
DN 129:269959
ED Entered STN: 21 Aug 1998
TI Ligands for DNA and RNA
AU Douglas, Kenneth T.
CS School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, M13 9PL, UK
SO Structure, Motion, Interaction and Expression of Biological Macromolecules, Proceedings of the Conversation in the Discipline Biomolecular Stereodynamics, 10th, Albany, June 17-21, 1997 (1998), Meeting Date 1997, Volume 1, 279-293. Editor(s): Sarma, Ramaswamy H.; Sarma, Mukti H. Publisher: Adenine Press, Schenectady, N. Y.
CODEN: 66NGAV
DT Conference
LA English
CC 1-3 (Pharmacology)
AB In contrast to rational drug and ligand design based on mol. graphics for the field of proteins, the situation for nucleic acid ligand design is less advanced, but is now proceeding rapidly. For DNA the aspect most developed in this sense is the minor groove, but for RNA there is still rather little in the way of ligand design reported. Insight into the DNA minor groove has reached the stage at which it is now possible to test the

possibility of rational ligand design in a number of objective ways. The first stage of this is to rationalize observations already made, but more rigorous is to test the ability to predict structural and chemical properties. In this contribution the ability to predict binding interactions for ligands in the minor groove of B-DNA of a series of analogs of Hoechst 33258 will be analyzed. These compds. were designed using mol. graphic/dynamics based on high-field NMR structural determination of Hoechst-duplex DNA complexes using a synthetic oligonucleotide sequence. Enthalpy and entropy contributors to net binding strength will be considered. The test of prediction powers is not merely to be able to achieve better net ligand binding strength, but also to propose specific bonding interactions. These predictions have been probed structurally using NMR anal. at high resolution of ligand-DNA complexes, again designed by mol. modeling. As well as using structural probes such as NMR spectroscopy, it is possible to test predictive ability by introducing novel chemical reactivity. In this context we shall describe a novel DNA strand-cleaving method, designed using mol. graphics of the above structures to locate a transition metal ion binding site very specifically and close to the phosphodiester backbone, allowing the generation of reactive free radicals to effect cleavage. Relative to DNA, RNA-binding ligands are less widely studied at present and, in the final part of the contribution, the binding properties of some new ligands for tRNA, binding with 1:1 stoichiometry and low micromolar dissociation consts. will be described. Their binding has been studied by UV-visible spectrophotometry, fluorescent titration and NMR spectroscopy.

ST DNA RNA ligand structure modeling

IT Simulation and Modeling, biological
Structure-activity relationship
(mol. modeling of ligands for DNA and RNA)

IT Ligands
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(mol. modeling of ligands for DNA and RNA)

IT DNA
RNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mol. modeling of ligands for DNA and RNA)

IT 23491-45-4, Hoechst 33258 **23491-53-4** 39389-47-4, Distamycin
90991-94-9 132869-83-1 171782-32-4 171782-33-5 213974-59-5
213974-61-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(mol. modeling of ligands for DNA and RNA)

RE.CNT 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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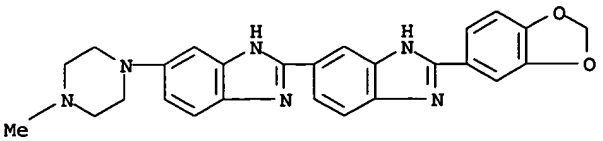
IT **23491-53-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(mol. modeling of ligands for DNA and RNA)

RN 23491-53-4 HCAPLUS

CN 2,5'-Bi-1H-benzimidazole, 2'-(1,3-benzodioxol-5-yl)-5-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



L28 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1998:512965 HCAPLUS

DN 129:239452

ED Entered STN: 19 Aug 1998

TI Molecular modeling and footprinting studies of DNA minor groove binders: bisquaternary ammonium heterocyclic compounds

AU Slickers, P.; Hillebrand, M.; Kittler, L.; Lober, G.; Suhnel, J.

CS Inst. Mol. Biotechnol., Jena, D-07708, Germany

SO Anti-Cancer Drug Design (1998), 13(5), 463-488
CODEN: ACDDEA; ISSN: 0266-9536

PB Oxford University Press

DT Journal

LA English

CC 1-3 (Pharmacology)
Section cross-reference(s): 22
AB The authors report new quant. footprinting data which reveal differences in binding consts. of bisquaternary ammonium heterocyclic compds. (BQA) with AT-rich DNA sites depending on the ligand structure and on the size and sequence of the DNA binding site. To understand the dependence of binding affinity on the ligand structure the authors have performed quantum-chemical AM1 calcns. on the BQA compds. and on subunits to explore the conformational space and to calculate the electronic and structural features of individual ligand conformations. Due to the properties of the rotatable backbone bonds, there is a large number of possible conformations with almost equal energy. The authors present a new method for the calcn. of the radius of curvature of mol. structures. Assuming that strong binders should have a shape complementary to the DNA minor groove, this measure is used to select the optimum conformations for DNA-drug binding. The approach yields the correct ligand conformation for SN6999, for which an x-ray DNA-drug structure is known. The curvature of the optimum conformations of all ligands is compared with the exptl. binding consts. A correlation is found between curvature and binding constant provided other structural factors do not vary. Therefore, the authors conclude that within structurally similar BQA compds., the extent of curvature is the relevant quantity which modulates the binding affinity.
ST DNA minor groove binder heterocyclic compd; bisquaternary ammonium heterocyclic compd DNA binding; mol modeling DNA binding heterocyclic compd; QSAR DNA binding heterocyclic compd
IT Bond angle
(dihedral; mol. modeling and footprinting studies of DNA minor groove binders using bisquaternary ammonium heterocyclic compds.)
IT AM1 MO (molecular orbital)
Bond length
Conformation
Electrostatic potential
Molecular association
Molecular modeling
QSAR (structure-activity relationship)
(mol. modeling and footprinting studies of DNA minor groove binders using bisquaternary ammonium heterocyclic compds.)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(mol. modeling and footprinting studies of DNA minor groove binders using bisquaternary ammonium heterocyclic compds.)
IT Bond angle
(torsional; mol. modeling and footprinting studies of DNA minor groove binders using bisquaternary ammonium heterocyclic compds.)
IT 14120-88-8, SN4094 18355-40-3, SN6570 23491-45-4, Hoechst 33258 23617-49-4, SN6324 23647-94-1, SN5754 47165-04-8, DAPI 47853-44-1, SN6113 53222-25-6, SN7167 68772-09-8, SN6999 68772-49-6, SN18071 88476-80-6, SN 6053 132869-83-1 146426-41-7, SN6131 146426-42-8, SN6132 163228-16-8 163228-20-4 **213137-22-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(mol. modeling and footprinting studies of DNA minor groove binders using bisquaternary ammonium heterocyclic compds.)
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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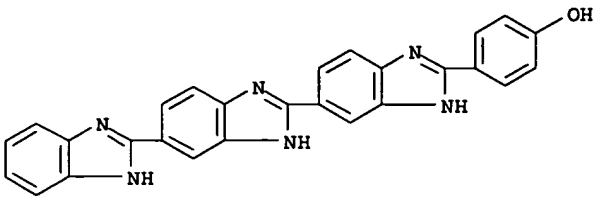
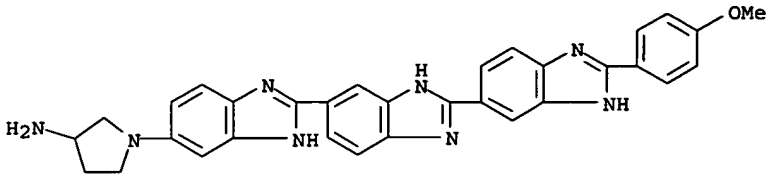
IT **213137-22-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(mol. modeling and footprinting studies of DNA minor groove binders using bisquaternary ammonium heterocyclic compds.)
RN 213137-22-5 HCAPLUS
CN Phenol, 4-[2,5':2',5''-ter-1H-benzimidazol]-2''-yl- (9CI) (CA INDEX NAME)



L28 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:607536 HCAPLUS
DN 125:265169
ED Entered STN: 12 Oct 1996
TI Isohelicity and Phasing in Drug-DNA Sequence Recognition: Crystal Structure of a Tris(benzimidazole)-Oligonucleotide Complex
AU Clark, George R.; Gray, Emily J.; Neidle, Stephen; Li, Yu-Hua; Leupin, Werner
CS CRC Biomolecular Structure Unit, Institute of Cancer Research, Sutton/Surrey, SM2 5NG, UK
SO Biochemistry (1996), 35(43), 13745-13752
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The crystal structure is reported of a tris(benzimidazole) analog of the minor-groove drug Hoechst 33258 bound to the sequence d(CGCAAATTTGCG)2. The structure has been refined to an R factor of 17.4% at a resolution of 2.2 .ANG.. The ligand covers .apprx.71/2 base pairs, including the 5'-AAATTT central sequence. This has an exceptionally narrow minor-groove width, together with high propeller twists for individual base pairs. The ligand has a highly twisted structure, with an overall twist of 50.degree. between aromatic rings. All three benzimidazole subunits are in register with the DNA, and there is a sym. group of six hydrogen bonds between ligand and A.cntdot.T base-pair edges. By contrast, the ligand does not show an optimal isohelical fit to the DNA. The correct phasing of drug and DNA base pairs is ensured by a number of changes to the DNA such that the central 5'-AAATTT region is slightly unwound relative to the structures of other noncovalent minor-groove drug complexes.
ST drug DNA sequence recognition crystal structure; trisbenzimidazole oligonucleotide complex crystal structure
IT Crystal structure
Hydrogen bond
(isohelicity and phasing in drug-DNA sequence recognition using crystal structure of a benzimidazole-oligonucleotide complex)
IT Deoxyribonucleic acids
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(isohelicity and phasing in drug-DNA sequence recognition using crystal structure of a benzimidazole-oligonucleotide complex)
IT 149318-33-2 **182496-21-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(isohelicity and phasing in drug-DNA sequence recognition using crystal structure of a benzimidazole-oligonucleotide complex)
IT **182496-22-6**
RL: FMU (Formation, unclassified); PRP (Properties); FORM (Formation, nonpreparative)
(isohelicity and phasing in drug-DNA sequence recognition using crystal structure of a benzimidazole-oligonucleotide complex)
IT **182496-21-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(isohelicity and phasing in drug-DNA sequence recognition using crystal structure of a benzimidazole-oligonucleotide complex)
RN 182496-21-5 HCAPLUS
CN 3-Pyrrolidinamine, 1-[2''-(4-methoxyphenyl)[2,5':2',5''-ter-1H-benzimidazol]-5-yl]- (9CI) (CA INDEX NAME)



IT **182496-22-6**
RL: FMU (Formation, unclassified); PRP (Properties); FORM (Formation, nonpreparative)
(isohelicity and phasing in drug-DNA sequence recognition using crystal structure of a benzimidazole-oligonucleotide complex)
RN 182496-22-6 HCAPLUS
CN Guanosine, 2'-deoxycytidylyl-(5'.fwdarw.3')-2'-deoxyguanylyl-(5'.fwdarw.3')-2'-deoxycytidylyl-(5'.fwdarw.3')-2'-deoxyadenylyl-(5'.fwdarw.3')-2'-deoxyadenylyl-(5'.fwdarw.3')-2'-deoxyadenylyl-(5'.fwdarw.3')-thymidinylyl-(5'.fwdarw.3')-thymidylyl-(5'.fwdarw.3')-thymidylyl-(5'.fwdarw.3')-2'-deoxyguanylyl-(5'.fwdarw.3')-2'-deoxycytidylyl-(5'.fwdarw.3')-2'-deoxy-, double-stranded complementary, compd. with 1-[2''-(4-methoxyphenyl)[2,5':2',5''-ter-1H-benzimidazol]-5-yl]-3-pyrrolidinamine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 182496-21-5
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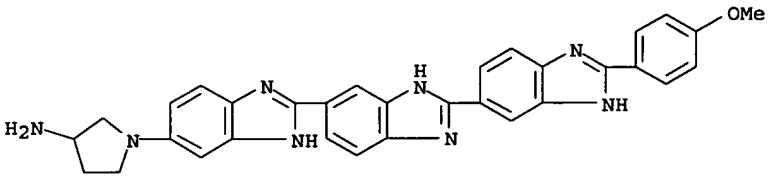


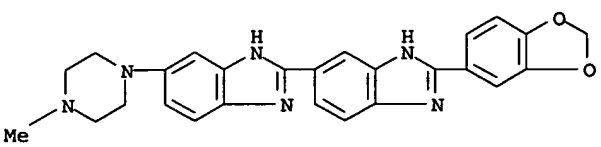
CM 2

CRN 146217-99-4
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L28 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1975:112032 HCAPLUS
DN 82:112032
ED Entered STN: 12 May 1984
TI Basic substituted 2,6-bisbenzimidazole derivatives, a novel series of substances with chemotherapeutic activity
AU Loewe, H.; Urbanietz, J.
CS Hoechst A.-G., Frankfurt/Main, Fed. Rep. Ger.
SO Arzneimittel-Forschung (1974), 24(12), 1927-33
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA German
CC 28-18 (Heterocyclic Compounds (More Than One Hetero Atom))
GI For diagram(s), see printed CA Issue.
AB Reaction of 2,5-O2NClC6H3NH2 with RH [R = R1 (with R2 = Me, Et, CHMe2, Bu, CH2Ph, CH2CH2OH, CO2Et, CH2CH2NEt2, Ph, CONEt2, or 2-pyridinyl), piperidino, morpholino, or NEt2] gave 2,5-O2NRC6H3NH2, which were reduced to give 3,4-(H2N)2-C6H3R (I). I reacted with 3,4-O2N(H2N)C6H3C(:NH)OEt.HCl to give the benzimidazoles II (R3 = NO2), reduction of which over Raney Ni gave II (R3 = NH2), which reacted with 2,3,4-R6-R4R5C6H2C(:NH)OEt.HCl to give III (R4 = H, Cl, Me, NO2, or OMe; R5 = H, OMe, OEt, OPr, OBu, Me, Cl, NMe2, NH2 OPh, Ph, NO2, or OH; or R4R5 = OCH2O; R6 = H or OH). III had anthelmintic activity, especially against filarias in cotton rats. In addition III showed fluorochromic properties.
ST benzimidazole piperazinylbis anthelmintic; piperazinylbisbenzimidazole

anthelmintic
IT Anthelmintics
(2,6'-bibenzimidazoles as)
IT 54998-08-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction with aminonitrobenzimidoyl ethyl ether)
IT 23470-57-7P 23470-58-8P 23470-59-9P 23470-60-2P 23470-62-4P
23491-49-8P 23617-82-5P 23617-83-6P 54998-09-3P 54998-10-6P
54998-26-4P 54998-27-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction with benzimidoyl ethyl ether)
IT 23470-40-8P 23470-41-9P 23470-42-0P 23470-43-1P 23470-44-2P
23470-45-3P 23470-47-5P 23470-49-7P 23470-50-0P 23470-51-1P
23470-52-2P 23470-53-3P 23470-54-4P 23470-56-6P 23491-48-7P
54997-96-5P 54997-97-6P 54997-98-7P 54997-99-8P 54998-00-4P
54998-01-5P 54998-02-6P 54998-03-7P 54998-04-8P 54998-05-9P
54998-06-0P 54998-07-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of)
IT 23470-26-0P 23470-27-1P 23470-28-2P 23470-29-3P 23470-30-6P
23470-31-7P 23470-33-9P 23491-44-3P 23491-50-1P 23491-51-2P
23491-52-3P **23491-53-4P** 23491-54-5P 23554-98-5P
23554-99-6P 23555-00-2P 23555-01-3P 23555-02-4P 23617-78-9P
23623-06-5P 23623-07-6P 23623-08-7P 23651-51-6P 23651-52-7P
23685-00-9P 23813-09-4P 54998-11-7P 54998-12-8P 54998-13-9P
54998-14-0P 54998-15-1P 54998-16-2P 54998-17-3P 54998-18-4P
54998-19-5P 54998-20-8P 54998-21-9P 54998-22-0P 54998-23-1P
54998-24-2P 54998-25-3P 55038-64-7P 55038-65-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
IT 4278-03-9 40546-41-6 40546-45-0 54998-35-5 54998-36-6 54998-37-7
54998-38-8 54998-39-9 54998-40-2 54998-41-3 54998-42-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with (diaminophenyl)piperazinobenzimidazoles)
IT 5333-86-8 43002-64-8 51618-01-0 54998-28-6 54998-29-7 54998-30-0
54998-31-1 54998-32-2 54998-33-3 54998-34-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with (dimethylaminophenyl)piperazinobenzimidazoles)
IT 92-54-6 103-76-4 109-01-3 110-91-8 119-54-0 120-43-4 2759-28-6
4038-92-0 4318-42-7 5308-25-8 5610-49-1 34803-66-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with chloronitroaniline)
IT 1635-61-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with piperazines)
IT 109-89-7, reactions 110-89-4, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(with chloronitroaniline)
IT **23491-53-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 23491-53-4 HCAPLUS
CN 2,5'-Bi-1H-benzimidazole, 2'-(1,3-benzodioxol-5-yl)-5-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



L28 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1969:481418 HCAPLUS
DN 71:81418
ED Entered STN: 12 May 1984
TI Piperazino bisbenzimidazoles
PA Farbwerke Hoechst A.-G.
SO Fr., 14 pp.
CODEN: FRXXAK

DT Patent
LA French
IC C07D; A61K
CC 28 (Heterocyclic Compounds (More Than One Hetero Atom))
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 1519964		19680405		
	DE 1670684			DE	
	GB 1186723			GB	
	US 3538097		19700000	US	
PRAI	DE		19660401		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
FR 1519964	IC	C07DIC A61K

GI For diagram(s), see printed CA Issue.

AB A variety of methods may be used to prepare the title compds. (I). Thus, heating 50 g. 5-chloro-2-nitroacetanilide, 30 g. 1-methylpiperazine, and 33 g. K2CO3 in 50 ml. Me2NCHO 4 hrs., addition of 300 ml. H2O, dissoln. of the precipitate in dilute HCl, and repptn. by basification gave 54 g. 5-(1-methyl-4-piperazinyl)-2-nitroacetanilide, m. 135.degree., hydrolysis of which gave 44 g. 5-(1-methyl-4-piperazinyl)-2-nitroaniline (II), m. 155.degree.. Hydrogenation of 40 g. II on Ni in 120 ml. MeOH gave 5-(1-methyl-4-piperazinyl)-1,2-diaminobenzene (III). A mixture of crude III with 51 g. 3,4-(O2N)(H2N)C6H3C(:NH)OEt.HCl (IIa) and 300 ml. HOAc was heated 6 hrs. on a H2O bath to give 55 g. 2-(3-nitro-4-aminophenyl)-6-(1-methyl-4-piperazinyl)benzimidazole (IV), m. 183-5.degree.. Hydrogenation of 30 g. IV on Ni in 150 ml. N HOAc at 90.degree. gave 18 g. 2-(3,4-diaminophenyl)-6-(1-methyl-4-piperazinyl)benzimidazole (V), m. 268.degree.. V (205 g.) and 160 g. 4-HOC6H4C(:NH)OEt.HCl in 1 l. HOAc was heated 2 hrs. under N on a steam bath giving 110 g. 2-[2-(4-hydroxyphenyl)-6-benzimidazolyl]-6-(1-methyl-4-piperazinyl)benzimidazole (I, Ar = HOC6H4, R1 = Me, R2 = H) (Ia) dihydrate; anhydride m. 235.degree. (decomposition); Ia.3HCl, decomposing 280.degree.; Ia.H3PO4, decomposing 315.degree.. Other I (R1 = Me, R2 > H) prepared were (Ar, m.p. anhydrous form, and composition of hydrate given): 2-HOC6H4, >200.degree., I.H2O; 4-MeOC6H4, 255.degree., I.1.5H2O; 3-Me-OC6H4, 220.degree., I.0.5H2O; 4-PrOC6H4, 286.degree., I.H2O; 4-EtOC6H4, 268.degree., I.1.5H2O; 4-BuOC6H4, 270.degree., I.0.5H2O.0.5EtOH; 3,4-CH2O2C6H3, >200.degree., I.2H2O; Ph, 190.degree. (di-Bz derivative m. 247.degree.), I.H2O.0.33PrOH; 4-MeC6H4, >200.degree., I.H2O.0.5EtOH; 3-Me-C6H4, 236.degree., I.H2O; 4-ClC6H4, >200.degree., I.1.5H2O; 4-Me2NC6H4, 210.degree., I.2H2O; 3-chloro-4-methylphenyl, >200.degree., I.H2O; 4-chloro-3-methylphenyl, 256.degree., -; 3-nitro-4-aminophenyl, 240.degree., I.2H2O; 4-PhC6H4, 310.degree., I.H2O; 2-naphthyl, 245.degree., I.0.5H2O; 3-nitro-4-(2-diethylaminoethylamino)phenyl, 294.degree., I.0.5H2O; and 4-NO2C6H4 (Ib), 210.degree., I.3H2O. By similar methods, 50 g. 6-chloro-3-nitro-4-acetamidotoluene and 30 g. 1-methylpiperazine gave 44 g. 4-methyl-5-(1-methyl-4-piperazinyl)-2-nitroacetanilide, m. 166.degree., hydrolysis of which gave 4-methyl-5-(1-methyl-4-piperazinyl)-2-nitroaniline (VI), m. 208.degree.. VI and IIa gave 2-(3-nitro-4-aminophenyl)-5-methyl-6-(1-methyl-4-piperazinyl)benzimidazole, m. 280.degree., which was hydrogenated to give 2-(3,4-diaminophenyl)-5-methyl-6-(1-methyl-4-piperazinyl) benzimidazole (VII), m. 155.degree.. VII (11.3 g.) and 8 g. 4-methoxybenzimino ether hydrochloride in 80 ml. HOAc gave 10.3 g. 2-[2-(4-methoxyphenyl)-6-benzimidazolyl]-5-methyl-6-(1-methyl-4-piperazinyl)benzimidazole (I, Ar = 4-MeOC6H4, R1 = R2 = Me) sesquihydrate; anhydride m. 196.degree.. Compds. prepared in similar sequences were: 4-chloro-5-(1-methyl-4-piperazinyl)-2-nitroacetanilide, m. 150.degree., 4-chloro-5-(1-methyl-4-piperazinyl)-2-nitroaniline, m. 202.degree., 4-chloro-5-(1-methyl-4-piperazinyl)-1,2-diaminobenzene, 2-(3-nitro-4-aminophenyl)-5-chloro-6-(1-methyl-4-piperazinyl)benzimidazole, m. 258.degree., and 2-[2-(4-methoxyphenyl)-6-benzimidazolyl]-5-chloro-6-(1-methyl-4-piperazinyl)benzimidazole (I, Ar = 4-MeOC6H4, r1 = Me, R2 = Cl) tetrahydrate; anhydride m. 207.degree.; 5-(1-ethyl-4-piperazinyl)-2-nitroacetanilide, m. 102.degree., 5-(1-ethyl-4-piperzinyl)-2-nitroaniline, m. 125.degree., 5-(1-ethyl-4-piperazinyl)-1,2-diaminobenzene, 2-(3-nitro-4-aminophenyl)-6-(1-ethyl-4-piperazinyl)benzimidazole, m. 188.degree., 2-(3,4-diaminophenyl)-6-(1-methyl-4-piperazinyl)benzimidazole, m. 170.degree., and 2-[2-(4-methoxyphenyl)-6-benzimidazolyl]-6-(1-ethyl-4-piperazinyl)benzimidazole, m. 188.degree. (monohydrate); 5-(1-isopropyl-4-piperazinyl)-2-nitroacetanilide, m. 87.degree., 5-(1-isopropyl-4-piperazinyl)-2-nitroaniline, m. 127.degree., 5-(1-isopropyl-4-piperazinyl)-1,2-diaminobenzene, m. 131.degree.,

2-(3-nitro-4-aminophenyl)-6-(1-isopropyl-4-piperazinyl)benzimidazole, m. 199.degree., 2-(3,4-diaminophenyl)-6-(1-isopropyl-4-piperazinyl)benzimidazole, m. 284.degree., and 2-[2-(4-methoxyphenyl)-6-benzimidazolyl]-6-(1-isopropyl-4-piperazinyl)benzimidazole, m. 214.degree. (dihydrate-hemiisopropylate); 5-(1-butyl-4-piperazinyl)-2-nitroacetanilide, m. 89.degree., 5-(1-butyl-4-piperazinyl)-2-nitroaniline, m. 110.degree., 5-(1-butyl-4-piperazinyl)-1,2-diaminobenzene, 2-(3-nitro-4-aminophenyl)-6-(1-butyl-4-piperazinyl)benzimidazole, m. 170.degree., 2-(3,4-diaminophenyl)-6-(1-butyl-4-piperazinyl)benzimidazole, m. 267.degree., and 2-[2-(4-methoxyphenyl)-6-benzimidazolyl]-6-(1-butyl-4-piperazinyl)benzimidazole, m. 260.degree. (sesquihydrate); 5-(1-benzyl-4-piperazinyl)-2-nitroacetanilide, m. 136.degree.; 5-(1-benzyl-4-piperazinyl)-2-nitroaniline, m. 162.degree., 5-(1-benzyl-4-piperazinyl)-1,2-diaminobenzene, 2-(3-nitro-4-aminophenyl)-6-(1-benzyl-4-piperazinyl)benzimidazole, m. 170.degree., 2-(3,4-diaminophenyl)-6-(1-benzyl-4-piperazinyl)benzimidazole, m, 206.degree., and 2-[2-(4-methoxyphenyl)-6-benzimidazolyl]-6-(1-benzyl-4-piperazinyl)-benzimadazole, m. 169.degree. (hemihydrate); 2-[2-(4-methoxyphenyl)-6-benzimidazolyl]-6-(4-piperazinyl)benzimidazole (by hydrogenolysis of the preceeding compound), m. 267.degree. (3.5H2O); 5-[1-(2-hydroxyethyl)-4-piperazinyl]-2-nitroacetanilide, m. 157.degree., 5-[1-(2-hydroxyethyl)-4-piperazinyl]-2-nitroaniline, m. 160.degree., 5-[1-(2-hydroxyethyl)-4-piperazinyl]-1,2-diaminobenzene, 2-(3-nitro-4-aminophenyl)-6-[1-(2-hydroxyethyl)-4-piperazinyl]benzimidazole, m. 120.degree., 2-(3,4-diaminophenyl)-6-[1-(2-hydroxyethyl)-4-piperazinyl]benzimidazole, m. 200.degree.; and 2-[2-(4-methoxyphenyl)-6-benzimidazolyl]-6-[1-(2-hydroxyethyl)-4-piperazinyl]benzimidazole, m. 190.degree. (sesquihydrate); 5-(1-ethoxycarbony Hydrogenation of 28 g. Ib in 400 ml. MeOH on Ni gave 18 g. 2-[2-(4-aminophenyl)-6-benzimidazolyl]-6-(1-methyl-4-piperazinyl)benzimidazole, m. 230.degree. (sesquihydrate). I have anthelminthic activity.

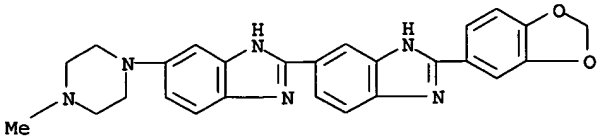
ST bibenzimidazoles piperazino; piperazino bibenzimidazoles; anthelmintic bibenzimidazoles

IT 23470-19-1P 23470-20-4P 23470-21-5P 23470-22-6P 23470-23-7P
23470-24-8P 23470-25-9P 23470-26-0P 23470-27-1P 23470-28-2P
23470-29-3P 23470-30-6P 23470-31-7P 23470-32-8P 23470-33-9P
23491-44-3P 23491-45-4P 23491-46-5P 23491-47-6P 23491-48-7P
23491-49-8P 23491-50-1P 23491-51-2P 23491-52-3P **23491-53-4P**
23491-54-5P 23491-55-6P 23491-56-7P 23554-98-5P 23554-99-6P
23555-00-2P 23555-01-3P 23555-02-4P 23555-03-5P 23617-77-8P
23617-78-9P 23623-05-4P 23623-06-5P 23623-07-6P 23623-08-7P
23651-51-6P 23651-52-7P 23685-00-9P 23813-09-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

IT **23491-53-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 23491-53-4 HCAPLUS

CN 2,5'-Bi-1H-benzimidazole, 2'-(1,3-benzodioxol-5-yl)-5-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



L28 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1954:71716 HCAPLUS

DN 48:71716

OREF 48:12740f-g

ED Entered STN: 22 Apr 2001

TI Imidazole derivatives. VII. Preparation of sulfonic acids of benzimidazole by baking method

AU Efros, L. S.

SO Zhurnal Obshchei Khimii (1953), 23, 881-2
CODEN: ZOKHA4; ISSN: 0044-460X

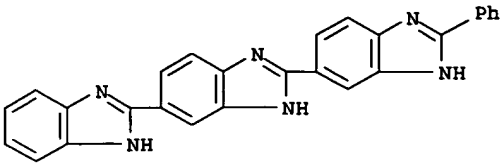
DT Journal

LA English

CC 10 (Organic Chemistry)

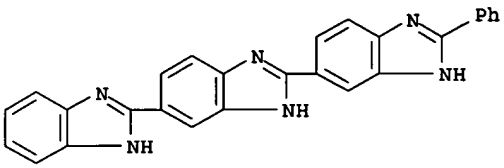
AB See C.A. 48, 4524c.

IT Blood
(-coagulation-inhibiting substances)
IT Spectra
(of benzimidazole derivs. and polybenzimidazoles)
IT 2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2'',5(or 2'',6)-dimethyl-, trihydrochloride
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-methyl-, trihydrochloride
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-phenyl-
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-phenyl-, dihydrochloride
5(or 6)-Benzimidazolecarboxylic acid
5(or 6)-Benzimidazolecarboxylic acid, sulfate
5(or 6)-Benzimidazolecarboxylic acid, 2-methyl-
5(or 6)-Benzimidazolecarboxylic acid, 2-phenyl-, hydrochloride
5(or 6)-Benzimidazolesulfonic acid
5(or 6)-Benzimidazolesulfonic acid, 2-methyl-
Benzimidazole, 2-(3,4-diaminophenyl)-
Benzimidazole, 2-[2-methyl-5(or 6)-benzimidazolyl]-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride
Benzimidazole, 2-methyl-, sulfate
Benzimidazole, 5(or 6)-(2-benzimidazolyl)-2-[2-methyl-5(or 6)-benzimidazolyl]-, trihydrochloride
Benzimidazole, 5(or 6)-(2-benzimidazolyl)-2-[2-phenyl-5(or 6)-benzimidazolyl]-
Benzimidazole, 5(or 6)-(2-benzimidazolyl)-2-[2-phenyl-5(or 6)-benzimidazolyl]-, dihydrochloride
Benzimidazole, 5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-2-[2-phenyl-5(or 6)benzimidazolyl]-
[2,5'(or 2,6')-Bibenzimidazole]-5(or 6)carboxylic acid, 2'-methyl-, dihydrochloride
[2,5'(or 2,6')-Bibenzimidazole]-5(or 6)carboxylic acid, 2'-phenyl-
[2,5'(or 2,6')-Bibenzimidazole]-5(or 6)carboxylic acid, 2'-phenyl-, hydrochloride
IT 288-32-4, Imidazole
(derivs.)
IT 51-17-2, Benzimidazole
(poly derivs.)
IT 615-15-6, Benzimidazole, 2-methyl- 41292-72-2, 2,5'(or 2,6')-Bibenzimidazole 59695-31-7, 1H-Tetrazole-5-carboxylic acid, 1-phenyl-, potassium salt 66630-70-4, 5(or 6)-Benzimidazolecarboxylic acid, 2-phenyl- 763140-09-6, 2,5'(or 2,6')-Bibenzimidazole, dihydrochloride **763140-22-3**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride **763140-28-9**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- **763140-45-0**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride **763140-62-1**, 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride 763932-97-4, 2,5'(or 2,6')-Bibenzimidazole, 2'-phenyl-, hydrochloride 763932-98-5, 2,5'(or 2,6')-Bibenzimidazole, 2'-phenyl- 763932-99-6, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-methyl-2'-phenyl-, hydrochloride 763933-00-2, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-methyl-2'-phenyl-
(preparation of)
IT 1076-38-6, Coumarin, 4-hydroxy-
(reactions of)
IT 51-17-2, Benzimidazole
(sulfonated derivs.)
IT **763140-22-3**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride **763140-28-9**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- **763140-45-0**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride **763140-62-1**, 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride
(preparation of)
RN 763140-22-3 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride (5CI) (CA INDEX NAME)

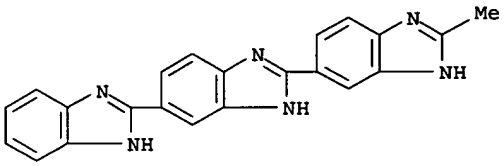


●2 HCl

RN 763140-28-9 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- (5CI) (CA INDEX NAME)

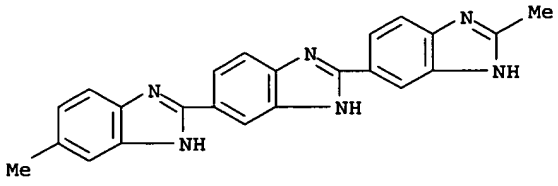


RN 763140-45-0 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride (5CI) (CA INDEX NAME)



●3 HCl

RN 763140-62-1 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride (5CI) (CA INDEX NAME)

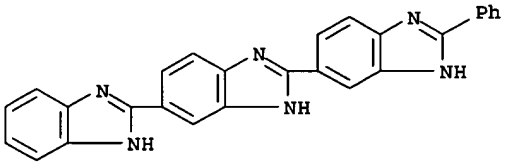


●3 HCl

L28 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1954:71715 HCAPLUS
DN 48:71715
OREF 48:12740f
ED Entered STN: 22 Apr 2001
TI Imidazole derivatives. VI. Synthesis of some polybenzimidazoles
AU Porai-Koshits, B. A.; Efros, L. S.; Boichinova, E. S.
SO Zhurnal Obshchei Khimii (1953), 23, 873-9

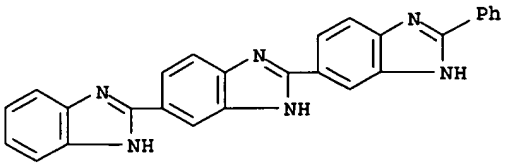
Search done by Noble Jarrell

CODEN: ZOKHA4; ISSN: 0044-460X
DT Journal
LA English
CC 10 (Organic Chemistry)
AB See C.A. 48, 4523d.
IT Spectra
(of benzimidazole derivs. and polybenzimidazoles)
IT 2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2'',5(or 2'',6)-dimethyl-, trihydrochloride
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-methyl-, trihydrochloride
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-phenyl-
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-phenyl-, dihydrochloride
IT 288-32-4, Imidazole
(derivs.)
IT 41292-72-2, 2,5'(or 2,6')-Bibenzimidazole 763140-09-6, 2,5'(or 2,6')-Bibenzimidazole, dihydrochloride **763140-22-3**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride **763140-28-9**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- **763140-45-0**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride **763140-62-1**, 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride 763932-97-4, 2,5'(or 2,6')-Bibenzimidazole, 2'-phenyl-, hydrochloride 763932-98-5, 2,5'(or 2,6')-Bibenzimidazole, 2'-phenyl- 763932-99-6, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-methyl-2'-phenyl-, hydrochloride 763933-00-2, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-methyl-2'-phenyl-
(preparation of)
IT **763140-22-3**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride **763140-28-9**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- **763140-45-0**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride **763140-62-1**, 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride
(preparation of)
RN 763140-22-3 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride (5CI) (CA INDEX NAME)

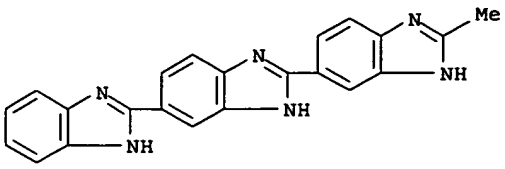


●2 HCl

RN 763140-28-9 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- (5CI) (CA INDEX NAME)

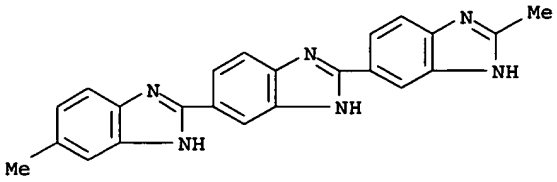


RN 763140-45-0 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride (5CI) (CA INDEX NAME)



●3 HCl

RN 763140-62-1 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride (5CI) (CA INDEX NAME)



●3 HCl

L28 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1954:71714 HCAPLUS
DN 48:71714
OREF 48:12739c-i,12740a-f
ED Entered STN: 22 Apr 2001
TI 1,2,4-Triazole analogs of histamine
AU Ainsworth, C.; Jones, R. G.
CS Lilly Research Labs., Indianapolis, IN
SO Journal of the American Chemical Society (1953), 75, 4915-18
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA Unavailable
CC 10 (Organic Chemistry)
OS CASREACT 48:71714
AB 3-(2-Aminoethyl)-1H-1,2,4-triazole (I) and several of its derivs. have been synthesized. I and, to a lesser degree, its 3-PhCH2NHCH2CH2 (II), 3-Me2CHNHCH2CH2 (III), and 3-AcNHCH2CH2 analogs (IV) exhibited a typical histaminelike activity and were effective orally. H2NCSNHNH2 (102 g.) and 700 cc. dry pyridine treated during 1-2 h. portion-wise with 237 g. .omicron.-C6H4(CO)2NCH2CH2COCl below 0.degree., the mixture let stand overnight, poured with stirring into 2 l. ice water, and the heavy white precipitate washed with 1 l. ice water, 1 l. 50% aqueous AcOH, and again 1 l. ice water yielded 235-50 g. (80-5%) .omicron.-C6H4(CO)2NHCH2CH2CONHNHCSNH2 (V), white needles, m. 238-9.degree. (decomposition) (from AcOH). V (292 g.), 60 g. NaOMe, and 2.5 l. absolute EtOH refluxed overnight, about 2 l. solvent evaporated in vacuo, the residue added with stirring to 2 l. ice water containing 125 cc. concentrated HCl, the mixture let stand, and the solid product washed with 500 cc. H2O, 200 cc. 50% aqueous AcOH, and 200 cc. glacial AcOH gave 140 g. (50%) 3-(2-phthalimidoethyl)-1H-1,2,4-triazole-5-thiol (VI), white needles, m. 295-7.degree. (from AcOH). VI (13.7 g.) suspended in 50 cc. H2O and treated with 10 cc. N2H4.H2O, the mixture let stand overnight at room temperature, and the resulting solid recrystd. from 200 cc. hot H2O yielded 4.5 g. (61%) 3-(2-aminoethyl)-1H-1,2,4-triazole-5-thiol, needles, m. 296-8.degree. (decomposition); the base dissolved in dilute HCl and the solution concentrated to dryness in vacuo gave the HCl salt, needles, m. 270.degree. (precipitated from MeOH with Et2O). VI (27.4 g.), 5.4 g. NaOMe, and 6.2 cc. MeI in 200 cc. EtOH refluxed 2 h., the solvent evaporated in vacuo, the residue extracted with 150 cc. hot EtOH, and the extract cooled deposited 20 g. 3-(2-phthalimidoethyl)-5-methylthio-1H-1,2,4-triazole (VII), dendritic crystals, m. 170-2.degree. (from H2O). VII (5.8 g.) and 3 cc. N2H4.H2O in 50 cc. H2O let stand overnight at room temperature, the mixture evaporated in vacuo,

the residue extracted with 100 cc. hot C6H6, the extract evaporated, the residue dissolved in EtOH, and the solution treated with dry HCl gave 3.2 g. (70%) di-HCl salt (VIII) of 3-(2-aminoethyl)-5-methylthio-1H-1,2,4-triazole, m. 218.degree. (decomposition) (from MeOH-Et2O). VII (5.8)and 50 cc. 6N HCl refluxed 6 h., the mixture cooled, filtered, and the filtrate evaporated in vacuo gave 76% VIII. VI (2.7 g.) in 100 cc. 10% aqueous AcOH treated 1 h. below 10.degree. with stirring with dry Cl, the resulting white solid filtered off, added directly to 100 cc. concentrated NH4OH, the solution evaporated on a steam bath overnight, the solid residue slurried with 50 cc. N HCl, and the product recrystd. from H2O gave 1.3 g. (40%) 3-(2-phthalimidoethyl)-1H-1,2,4-triazole-5-sulfonamide (IX), m. 280-2.degree. (decomposition). IX (3.2 g.), 3 cc. N2H4.H2O, and 50 cc. MeOH refluxed 0.5 h., the solvent removed in vacuo, the residue dissolved in 50 cc. H2O, the solution treated with 6N HCl, the precipitated phthalhydrazide filtered off, the filtrate evaporated to dryness, the residue treated with 50 cc. N NaOH, again taken to dryness in vacuo, and treated with 50 cc. 6N HCl, the solution evaporated to dryness, the residue extracted with EtOH, and the extract diluted with Et2O gave 3-(2-aminoethyl)-1H-1,2,4-triazole-5-sulfonamide-HCl, irregular white prisms, m. 170.degree. (decomposition), also obtained by the hydrolysis of IX with 6N HCl. To 100 cc. concentrated HNO3, 200 cc. H2O, and 1 g. NaNO2 was added below 45.degree. with stirring 100 g. VI in small portions, the mixture cooled to 0.degree., cautiously neutralized with saturated aqueous Na2CO3, and the precipitate washed with H2O to give 40 g. (43%) 3-(2-phthalimidoethyl)-1H-1,2,4-triazole (X), needles, m. 215.degree. (from H2O); HCl salt, m. 245.degree. (from MeOH-Et2O). VI dissolved in dilute aqueous NaOH, the solution acidified, and the product oxidized similarly with HNO3 gave no X. VI (1 g.) 3 teaspoonfuls Raney Ni, and 200 cc. EtOH refluxed 4 h., the hot mixture filtered, and the filtrate evaporated to dryness in vacuo gave X, white needles, m. 214-15.degree.. X (40 g.) and 500 cc. 6N HCl refluxed 8 h., the mixture cooled several hrs., filtered, the filtrate evaporated to dryness in vacuo, the residue dissolved in 500 cc. MeOH, and the solution treated with C and diluted with 1 l. Et2O gave 25-30 g. (84-97%) I.2HCl, decomposed at 251.degree.. I.2HCl (18.5 g.) in 100 cc. absolute EtOH refluxed 1 h. with 10.8 g. NaOMe, the mixture filtered, and the filtrate distilled gave 9 g. (80%) I, b0.1 158-60.degree., m. 83-5.degree.; dipicrate, yellow cubes, m. 190.degree. (from EtOH). I (11.2 g.), and 5.1 g. Me2CO in 100 cc. EtOH hydrogenated 6 h. over 0.1 g. PtO2 while heated with an IR lamp, the mixture filtered, the filtrate evaporated in vacuo, the residue in 50 cc. EtOH added to 46 g. picric acid in 300 cc. 95% EtOH, the solution cooled, and the solid deposit recrystd. twice from 300-cc. portions of 95% EtOH gave 45 g. (72%) dipicrate of III, m. 142-4.degree.; the dipicrate suspended in 200 cc. PhNO2, the mixture extracted with three 100-cc. portions of concentrated HCl, the extract washed with CHCl3, evaporated in vacuo, and the residue dissolved in MeOH and precipitated with Et2O gave III.2HCl, m. 186.degree.. I (3.4 g.) and 3.2 g. freshly distilled BzH in 50 cc. EtOH refluxed 2 h., the mixture hydrogenated over PtO2 at 40 lb. pressure, filtered, and the filtrate treated with 13.8 g. picric acid in 100 cc. hot EtOH gave 70% dipicrate of II, m. 115-17.degree. (from 50% aqueous EtOH), converted to II.2HCl, m. 220.degree.. I.2HCl (5.6 g.), 2.4 g. KOCN, and 2.5 g. NaHCO3 in 100 cc. H2O evaporated on the steam bath, the residue extracted with 50 cc. EtOH, and the extract diluted with 500 cc. Et2O gave 3-(2-ureidoethyl)-1H-1,2,4-triazole, m. 188-90.degree.. I.2HCl (5.5 g.) in 100 cc. 2N NaOH treated with stirring at 0.degree. with 2.8 g. BzCl, the mixture treated after 2 h. with 25 g. ice, adjusted with concentrated HCl to pH 5, and the precipitate washed with aqueous NaHCO3 and recrystd. from H2O gave 3.8 g. (55%) 3-(2-benzamidoethyl)-1H-1,2,4-triazole, feathery plates, m. 189-90.degree.. I.2HCl (5.5 g.) in 50 cc. 2N NaOH treated at 0.degree. with 2 cc. AcOH, the solution after 0.5 h. acidified with 6N HCl, evaporated to dryness, the residue extracted with 100 cc. warm absolute EtOH, and the extract diluted with 400 cc. Et2O gave IV.HCl, white solid, m. 160.degree.. I (1.7 g.) and 2 g. Ac2O in 50 cc. glacial AcOH heated 3 h. on the steam bath, the mixture diluted with 25 cc. H2O, let stand 15 min., concentrated to dryness in vacuo, the residue recrystd. from EtOH gave IV, needles, m. 215-16.degree..

IT Spectra
(of benzimidazole derivs. and polybenzimidazoles)

IT 2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2'',5(or 2'',6)-dimethyl-, trihydrochloride
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-methyl-, trihydrochloride
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-phenyl-
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-phenyl-, dihydrochloride
5(or 6)-Benzimidazolecarboxylic acid
5(or 6)-Benzimidazolecarboxylic acid, sulfate
5(or 6)-Benzimidazolecarboxylic acid, 2-methyl-
5(or 6)-Benzimidazolecarboxylic acid, 2-phenyl-, hydrochloride

5(or 6)-Benzimidazolesulfonic acid
5(or 6)-Benzimidazolesulfonic acid, 2-methyl-
Acetamide, N-2-s-triazol-3-ylethyl-
Benzamide, N-2-s-triazol-3-ylethyl-
Phthalimide, N-2-s-triazol-3-ylethyl-
Phthalimide, N-2-s-triazol-3-ylethyl-, hydrochloride
Phthalimide, N-[2-(5-mercapto-s-triazol-3-yl)ethyl]-
Phthalimide, N-[2-(5-sulfamoyl-s-triazol-3-yl)ethyl]-
Phthalimide, N-[2-[5-(methylthio)-s-triazol-3-yl]ethyl]-
Semicarbazide, 1-(3-phthalimidopropionyl)-3-thio-
Urea, (2-s-triazol-3-ylethyl)-
[2,5'(or 2,6')-Bibenzimidazole]-5(or 6)carboxylic acid, 2'-methyl-, dihydrochloride
[2,5'(or 2,6')-Bibenzimidazole]-5(or 6)carboxylic acid, 2'-phenyl-
[2,5'(or 2,6')-Bibenzimidazole]-5(or 6)carboxylic acid, 2'-phenyl-, hydrochloride
s-Triazole, 3-(2-acetamidoethyl)-
s-Triazole, 3-(2-acetamidoethyl)-, hydrochloride
s-Triazole, 3-(2-aminoethyl)-5-(methylthio)-, dihydrochloride
s-Triazole, 3-(2-benzamidoethyl)-
s-Triazole, 3-(2-ureidoethyl)-
s-Triazole-3-sulfonamide, 5-(2-aminoethyl)-, hydrochloride
s-Triazole-3-thiol, 5-(2-aminoethyl)-
s-Triazole-3-thiol, 5-(2-aminoethyl)-, hydrochloride
s-Triazole-3-thiol, 5-(2-phthalimidoethyl)-

IT s-Triazole, 3-(2-benzylaminoethyl)-
s-Triazole, 3-(2-isopropylaminoethyl)-
(and derivs.)

IT 2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 5(or 6)-methyl-2''-phenyl-
2,5'(or 2,6')-Bibenzimidazole, 2',5(or 2',6)-dimethyl-
2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-
2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-2'-phenyl-
(and salts)

IT 7728-75-8, s-Triazole, 3-(2-aminoethyl)-
(and derivs.)

IT 85-41-6, Phthalimide 288-32-4, Imidazole
(derivs.)

IT 288-88-0, s-Triazole
(histamine-related compds.)

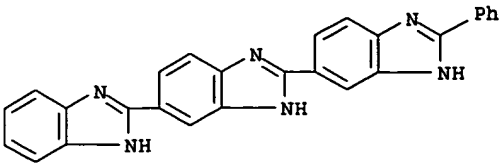
IT 51-17-2, Benzimidazole
(poly derivs., sulfonated derivs.)

IT 7730-80-5, Acetamide, N-2-s-triazol-3-ylethyl-, hydrochloride 41292-72-2, 2,5'(or 2,6')-Bibenzimidazole 66630-70-4, 5(or 6)-Benzimidazolecarboxylic acid, 2-phenyl- 763140-09-6, 2,5'(or 2,6')-Bibenzimidazole, dihydrochloride **763140-22-3**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride **763140-28-9**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- **763140-45-0**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride **763140-62-1**, 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride 763932-97-4, 2,5'(or 2,6')-Bibenzimidazole, 2'-phenyl-, hydrochloride 763932-98-5, 2,5'(or 2,6')-Bibenzimidazole, 2'-phenyl- 763932-99-6, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-methyl-2'-phenyl-, hydrochloride 763933-00-2, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-methyl-2'-phenyl-
(preparation of)

IT 51-45-6, Histamine
(triazole analogs of)

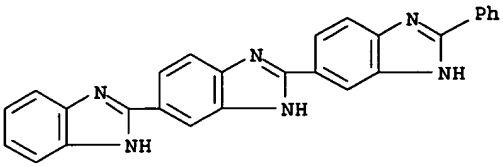
IT **763140-22-3**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride **763140-28-9**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- **763140-45-0**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride **763140-62-1**, 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride
(preparation of)

RN 763140-22-3 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride (5CI) (CA INDEX NAME)

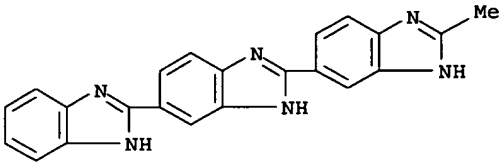


●2 HCl

RN 763140-28-9 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- (5CI) (CA INDEX NAME)

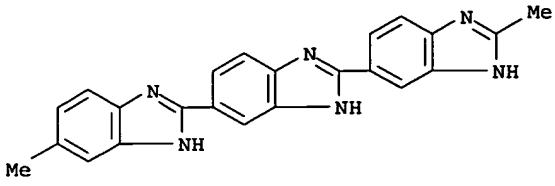


RN 763140-45-0 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride (5CI) (CA INDEX NAME)



●3 HCl

RN 763140-62-1 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride (5CI) (CA INDEX NAME)



●3 HCl

L28 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1954:25016 HCAPLUS
DN 48:25016
OREF 48:4523d-i,4524a-c
ED Entered STN: 22 Apr 2001
TI Imidazole derivatives. VI. Synthesis of some polybenzimidazoles
AU Porai-Koshits, B. A.; Efros, L. S.; Boichinova, E. S.
CS Lensovet Technol. Inst., Leningrad

Search done by Noble Jarrell

SO Zhurnal Obshchei Khimii (1953), 23, 835-41
CODEN: ZOKHA4; ISSN: 0044-460X
DT Journal
LA Unavailable
CC 10 (Organic Chemistry)
OS CASREACT 48:25016
AB cf. ibid. 697. To 1.32 g. 5-methylbenzimidazole in 10 ml. 1:3 H2SO4 was added dropwise at 100-3.degree. 2.4 g. chromic acid in 10 ml. H2SO4 (1:3) and the mixture chilled after 15 min., yielding 5-benzimidazolecarboxylic acid sulfate, which with NaOAc gave the free acid, m. 300-25.degree. (from H2O). This (1.62 g.) and 1.08 g. .omicron.-C6H4(NH2)2 in 10 ml. 20% HCl heated in sealed tube 4 hrs. at 180-200.degree., then neutralized with NH4OH and filtered, gave 5-(2'-benzimidazolyl)benzimidazole, isolated as the di-HCl salt, m. 362.degree. (from concentrated HCl); the free base could not be purified owing to the formation of gels. Similar oxidation of 2,5-dimethylbenzimidazole gave 70-5% 2-methyl-5-benzimidazolecarboxylic acid (I), m. 301-2.degree. (from H2O). This with .omicron.-C6H4(NH2)2 in 20% HCl as above gave after 40 min. at 180-200.degree. 2-methyl-5-(2'-benzimidazolyl)benzimidazole-2HCl, m. 339-40.degree. (from HCl), which with NH4OH gave the free base (II), m. 340.degree. (from dilute EtOH); this with NH4OH-AgNO3 in EtOH gave a flocculent di-Ag salt; the free base yields a dipicrate, m. 282-2.5.degree.. 3,4-(H2N)2C6H3Me (1.22 g.) and 1.76 g. I in 10 ml. 20% HCl heated in a sealed tube 4 hrs. at 180-200.degree. gave 2,5'-dimethyl-5-(2'-benzimidazolyl)benzimidazole, m. high and unsharp, which gave a di-HCl salt, m. above 360.degree. (from 25% HCl); the free base yields a picrate, m. 274.degree.. This oxidized with chromic acid as above gave 2-methyl-5-(5'-carboxy-2'-benzimidazolyl)benzimidazole-2HCl (III), m. about 350.degree. (from 15% HCl); this, decarboxylated by heating with sodalime at 300.degree. gave II (picrate, m. 274.degree.). III with .omicron.-C6H4(NH2)2 and 15% HCl 4 hrs. at 180-200.degree. gave 75% 2-methyl-5-[2'-benzimidazolyl-5'-(2''-benzimidazolyl)]benzimidazole-3HCl, m. above 360.degree. (from dilute HCl). Similarly condensation with 3,4-(H2N)2C6H3Me gave 85-90% 2,5'-dimethyl-5-[2'-benzimidazolyl-5'-(2''-benzimidazolyl)]benzimidazole-3HCl, m. about 400.degree. (from dilute HCl). 2-Phenyl-5-methylbenzimidazole with chromic acid in aqueous H2SO4 gave 2-phenyl-5-benzimidazolecarboxylic acid, isolated as the HCl salt, m. 304-5.degree. (from aqueous HCl). Electrometric titration of this gives 2 pH breaks; at 8.4 and a weak one whose position is unstated. This heated with .omicron.-C6H4(NH2)2 in 15% HCl in sealed tube 6 hrs. at 180-200.degree. gave 2-phenyl-5-(2'-benzimidazolyl)benzimidazole, m. 308-10.degree. (from dilute EtOH); HCl salt, m. 323-6.degree. (from dilute HCl). Similarly 3,4-(H2N)2C6H3Me gave 2-phenyl-5-(5'-methyl-2'-benzimidazolyl)benzimidazole, m. 329-31.degree. (from dilute EtOH); HCl salt, m. 311-15.degree. (from dilute HCl). This was oxidized as above to 2-phenyl-5-(5'-carboxy-2'-benzimidazolyl)benzimidazole, isolated as the HCl salt, m. 314-19.degree., which, heated with .omicron.-C6H4(NH2)2 and 10% HCl, gave 2-phenyl-5-[2'-benzimidazolyl-5'(2''-benzimidazolyl)]benzimidazole, isolated as the di-HCl salt, does not m. 360.degree. (from aqueous HCl). 3,4-(H2N)2C6H3Me gave 2-phenyl-5-[2'-benzimidazolyl-5'(5''-methyl-2''-benzimidazolyl)]benzimidazole, isolated as the di-HCl salt, does not m. 360.degree.; the free base is insol. in organic solvents except AcOH in which it forms the corresponding salt. Heating 2.25 g. 3,4-(H2N)2C6H3CO2H.HCl with .omicron.-C6H4(NH2)2 and 10 ml. 20% HCl in a sealed tube 40 min. at 180-200.degree. gave 0.1 g. 3,4-diaminophenylbenzimidazole, m. 325-30.degree. (from 10% HCl); this reacts with HNO2 without forming a diazonium salt; in AcOH it gives a green precipitate with phenanthrenequinone. Condensation with HCO2H or AcOH gave the previously described bis-benzimidazole derivs. (cf. C.A. 44, 1100b). Benzimidazoles have characteristic absorption maximum at 2700-800, dibenzimidazoles at 3100-200, and tribenzimidazoles at 3400-500 A.; even the latter absorb but weakly in the visible, being pale yellow.
IT Spectra
(of benzimidazole derivs. and polybenzimidazoles)
IT 2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2'',5(or 2'',6)-dimethyl-, trihydrochloride
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-methyl-, trihydrochloride
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-phenyl-
2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 2''-phenyl-, dihydrochloride
5(or 6)-Benzimidazolecarboxylic acid
5(or 6)-Benzimidazolecarboxylic acid, sulfate
5(or 6)-Benzimidazolecarboxylic acid, 2-methyl-
5(or 6)-Benzimidazolecarboxylic acid, 2-phenyl-, hydrochloride
Benzimidazole, 2-(3,4-diaminophenyl)-

Benzimidazole, 2-[2-methyl-5(or 6)-benzimidazolyl]-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride
Benzimidazole, 5(or 6)-(2-benzimidazolyl)-2-[2-methyl-5(or 6)-benzimidazolyl]-, trihydrochloride
Benzimidazole, 5(or 6)-(2-benzimidazolyl)-2-[2-phenyl-5(or 6)-benzimidazolyl]-
Benzimidazole, 5(or 6)-(2-benzimidazolyl)-2-[2-phenyl-5(or 6)-benzimidazolyl]-, dihydrochloride
Benzimidazole, 5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-2-[2-phenyl-5(or 6)benzimidazolyl]-
[2,5'(or 2,6')-Bibenzimidazole]-5(or 6)carboxylic acid, 2'-methyl-, dihydrochloride
[2,5'(or 2,6')-Bibenzimidazole]-5(or 6)carboxylic acid, 2'-phenyl-
[2,5'(or 2,6')-Bibenzimidazole]-5(or 6)carboxylic acid, 2'-phenyl-, hydrochloride

IT 2,5'(or 2,6')-2',5''(or 2',6'')-Terbenzimidazole, 5(or 6)-methyl-2''-phenyl-
2,5'(or 2,6')-Bibenzimidazole, 2',5(or 2',6)-dimethyl-
2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-
2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-2'-phenyl-
(and salts)

IT 288-32-4, Imidazole
(derivs.)

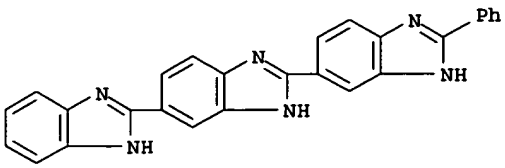
IT 51-17-2, Benzimidazole
(poly derivs.)

IT 41292-72-2, 2,5'(or 2,6')-Bibenzimidazole 66630-70-4, 5(or 6)-Benzimidazolecarboxylic acid, 2-phenyl- 763140-09-6, 2,5'(or 2,6')-Bibenzimidazole, dihydrochloride **763140-22-3**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride **763140-28-9**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- **763140-45-0**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride **763140-62-1**, 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride
763932-97-4, 2,5'(or 2,6')-Bibenzimidazole, 2'-phenyl-, hydrochloride
763932-98-5, 2,5'(or 2,6')-Bibenzimidazole, 2'-phenyl- 763932-99-6, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-methyl-2'-phenyl-, hydrochloride
763933-00-2, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-methyl-2'-phenyl-
(preparation of)

IT 51-17-2, Benzimidazole
(sulfonated derivs.)

IT **763140-22-3**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride **763140-28-9**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- **763140-45-0**, 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride **763140-62-1**, 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride
(preparation of)

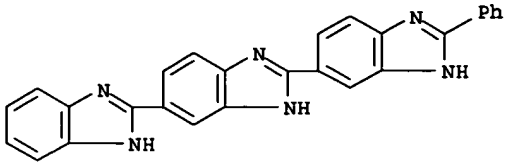
RN 763140-22-3 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl-, dihydrochloride (5CI) (CA INDEX NAME)



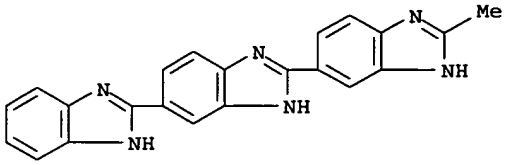
●2 HCl

RN 763140-28-9 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-phenyl- (5CI) (CA INDEX NAME)

Search done by Noble Jarrell

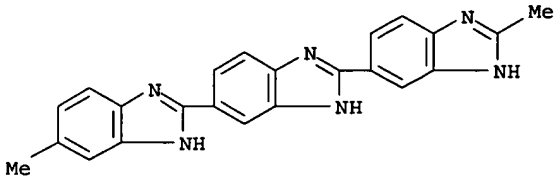


RN 763140-45-0 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 5(or 6)-(2-benzimidazolyl)-2'-methyl-, trihydrochloride (5CI) (CA INDEX NAME)



●3 HCl

RN 763140-62-1 HCAPLUS
CN 2,5'(or 2,6')-Bibenzimidazole, 2'-methyl-5(or 6)-[5(or 6)-methyl-2-benzimidazolyl]-, trihydrochloride (5CI) (CA INDEX NAME)



●3 HCl

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